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Analysis of Ventricular Repolarization Signals in Obstructive Sleep Apnea

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Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for any academic degree.

/Moonika Viigimäe/

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Ventrikulaarse repolarisatsiooni signaalide analüüs obstruktiivse uneapnoe korral

MOONIKA VIIGIMÄE

CONTENTS

LIST OF PUBLICATIONS

The current thesis is based on the following publications referred to in the text by their Roman numerals I – III.

I. **Viigimae, M.**, Karai, D., Pirn, P., Pilt, K., Meigas, K., Kaik, J. (2015). QT Interval Variability Index and QT Interval Duration in Different Sleep Stages: Analysis of Polysomnographic Recordings in Nonapneic Male Patients. – *Biomed Res Int*, vol 2015, ID 963028. (DOI: 10.1155/2015/963028).

II. **Viigimae, M.**, Karai, D., Pilt, K., Polo, O., Huhtala, H., Meigas, K., Kaik, J. (2017). Influence of gender on the QT interval variability and duration in different wake-sleep stages in non-sleep apneic individuals: Analysis of polysomnographic recordings. – *J Electrocardiol*, 50 (4), 444 – 449. (DOI: 10.1016/j.jelectrocard. 2017.03.012).

III. **Viigimae, M.**, Karai, D., Pilt, K., Pirn, P., Huhtala, H., Polo, O., Meigas, K., Kaik, J. (2017). QT interval variability index and QT interval duration during different sleep stages in patients with obstructive sleep apnea. – *Sleep Medicine*, 37, 160 – 167. (DOI: http://dx.doi.org/10.1016/ j.sleep. 2017.06.026).

Author´s Contribution to the Publications

The contribution by the author to the papers included in the thesis is as follows (Publications I – III):

- selecting patients;
- selecting appropriate epochs of sleep stages and electrocardiograms from polysomnographic recordings for processing;
- participating in statistical analysis;
- analyzing and interpreting data;
- writing the manuscript.

INTRODUCTION

Over the past decades, there has been a growing interest in certain breathing-related sleep disorders, especially obstructive sleep apnea (OSA), due to their established association with major cardiovascular diseases, cardiac arrhythmias, and sudden cardiac death (SCD) (Gami et al. 2013; Amino et al. 2016). In breathing-related sleep disorders, chronic sleep fragmentation and intermittent hypoxia shift the sympatho-vagal balance toward sympathetic predominance and vagal withdrawal (Palma et al. 2013), which may predispose to increased myocardial electrical instability. It has been determined that the major subgroups susceptible to adverse influences of surges in sympathetic activity during sleep are cardiac (Verrier and Josephson 2009) and OSA patients (Mehra et al. 2006).

Myocardial electrical instability, i.e. a predisposition to potentially life-threatening ventricular arrhythmias, can be indirectly assessed by non-invasive physiological parameters, including those reflecting ventricular repolarization inhomogeneity and prolongation. Non-invasive electrocardiographic (ECG) parameters such as increased QT interval variability and duration have been recognized as powerful predictors of arrhythmic events and SCD in population with heart disease (Atiga et al. 1998; Dobson et al. 2011; Fischer et al. 2015).

OSA-related arrhythmogenic risks have increasingly received attention by the medical community, at the same time, less information is available on QT interval properties in OSA patients (Baumert et al. 2008; Voigt et al. 2011; Kilicaslan et al. 2012). Even more, limited data is available concerning QT interval variability and duration changes in patients during various sleep stages. Our knowledge concerning the physiological effects of rapid-eye movement (REM) on the temporal QT variability is limited. Since REM sleep is characterized by sympathetic surges and elevated sympathetic tone influences both QT interval variability (Mine et al. 2008; Baumert et al. 2011) and duration (Merri et al. 1993), the assessment of modulatory effects of sleep stages on ventricular repolarization parameters per se can add more understanding to arrhythmia genesis in OSA patients. The gender dependence of the magnitude of elevated sympathetic drive during sleep in OSA patients is also less known.

There remains no general consensus on the proper use of QT interval parameters in clinical practice for evaluation of risk in patients with OSA (Dobson et al. 2013; Baumert et al. 2016). Prediction of ventricular arrhythmias and SCD in OSA patients represent an unmet medical need. More research must be done to develop a specific method for quantifying risk for malignant ventricular arrhythmias that can be integrated into routine diagnostic assessment of apneic patients in order to achieve an improvement in the patient's clinical management.

The general aim of this research was to investigate the ability of various mathematical algorithms to detect myocardial electrical instability in patients with and without obstructive sleep apnea by analysing polysomnographic recordings.

For this purpose, the QT variability index (Berger's QTVlog), QT interval correction formulas (the Bazett's equation, linear and parabolic heart rate correction formulas), and the Tpeak–Tend interval were applied in different sleep stages.

- The aim of **Publication I** was to study whether REM sleep affects QT interval variability and duration in patients without OSA.
- The aim of **Publication II** was to evaluate the gender difference of QT interval variability and duration in different sleep stages in non-apneic patients.
- The aim of **Publication III** was to determine which noninvasive quantitative measure of ECG is more useful to detect myocardial electrical instability in patients with OSA.

The doctoral thesis provides a general overview of the physiological basis of normal sleep, the current understanding of OSA pathophysiology in adults, and the standard diagnostic test for the diagnosis of OSA. A detailed discussion of the pathophysiology of OSA is beyond the scope of the present thesis, the focus is on the role of the autonomic nervous system. The thesis covers the clinical value and measurement principles of electrocardiographic QT interval parameters.

The novelty of the experimental study reported in this thesis lies in its methodological approach – the simultaneous application of the QT variability index (QTVI) and various QT interval correction (QTc) algorithms to polysomnographic ECG recordings at various sleep stages. The gender difference of QT interval variability and duration was evaluated in patients with and without OSA.

The ultimate goal of the study was to provide an appropriate screening measure that can be included into a sleep study to identify apneic patients with ventricular electrical instability. Appropriate referral to further cardiac evaluation for malignant ventricular arrhythmias may ensure an effective disease management and prevent sudden cardiac death.

Approbation

- **Viigimäe, M.**, Karai, D., Pirn, P., Pindmaa, M., Pilt, K., Meigas, K., Kaik, J. (2015). QT interval variability in different sleep stages. – *Proceedings of the 4th Cardiosleep International Congress, Paris*, 11.
- **Viigimäe, M.**, Karai, D., Pirn, P., Pindmaa, M., Pilt, K., Meigas, K,. Kaik, J. (2015). Assessment of ventricular repolarization prolongation and inhomogeneity reflecting parameters in different sleep stages. – *Proceedings of the EHRA EUROPACE-CARDIOSTIM 2015 Congress, Milano*, 40935.
- **Viigimae, M.**, Karai, D., Meigas, K., Kaik, J. (2017). QT interval variability index during different sleep stages in patients with obstructive sleep apnea. – *Proceedings of the 17th Nordic Sleep Conference, Tallinn*, 72 (P21).

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea index
ANS	autonomic nervous system
BMI	body mass index
ECG	electrocardiography
EEG	electroencephalography
HR	heart rate
HRV	heart rate variability
NREM	non-rapid eye movement sleep
OSA	obstructive sleep apnea
PNA	parasympathetic-nerve activity
PNS	parasympathetic nervous system
PSG	polysomnography
QTc	corrected QT interval
QT/RR	QT interval and heart rate relationship
QTV	QT-interval variability
QTVI	QT interval variability index
QTVN	normalized QT variability
Tp-e	Tpeak–Tend interval
REM	rapid-eye movement sleep
RR	interval between two R waves in the ECG
SCD	sudden cardiac death
SNA	sympathetic-nerve activity
SNS	sympathetic nervous system

TERMS

- **Apnea-hypopnea index** – The number of apneas and hypopneas per hour during sleep; a measure of the severity of sleep apnea.
- **Arousal** – Transient awakening from sleep (an abrupt shift of EEG frequency) lasting at least 3 seconds.
- **Autonomic nervous system** – The part of the nervous system that consists of two physiologically and anatomically distinct, mutually antagonistic components: the sympathetic and parasympathetic parts.
- **Hypoxia** – A state in which oxygen supply is insufficient.
- **Myocardium** – The muscle tissue of the heart (cardiac muscle, heart muscle).
- **Oxygen saturation** – The level of blood oxygen; refers to the fraction of oxygen-saturated hemoglobin (the molecule in red blood cells) relative to total hemoglobin (unsaturated + saturated) in the blood.
- **Oxygen desaturation** – Reduction in oxyhemoglobin saturation, usually as a result of an apnea or hypopnea.
- **Parasympathetic nervous system** – The part of the autonomic nervous system; inhibits or opposes the physiological effects of the sympathetic nervous system, slows the heart rate and dilates blood vessels.
- **Repolarization** – The return of cell membrane potential to resting potential after depolarization.
- **Sudden cardiac death** – An unexpected death due to heart problems, which occurs within on hour from the start of cardiac-related symptoms; the most common arrhythmias in the events of sudden cardiac death are ventricular fibrillation and sustained ventricular tachycardia.
- **Sympathetic nervous system** – The part of the autonomic nervous system; inhibits or opposes the physiological effects of the parasympathetic nervous system, speeds up the heart and contracts blood vessels.
- **Ventricle** – The part of the heart from which blood passes into the arteries.

1. PHYSIOLOGICAL BASIS OF SLEEP

Sleep is a complex and dynamic process. Effects of normal sleep are related to circadian variations and sleep stages.

Physiological sleep can be divided into non-rapid eye movement (NREM) and rapid eye movement (REM) stages. The normal human adult enters sleep through NREM sleep. NREM sleep is currently distinguished into three stages according to the American Academy of Sleep Medicine (AASM) scoring rules (Berry et al. 2017). The sleep stages are defined based on the electroencephalogram (EEG). Stage N1 (NREM 1) and N2 (NREM 2) are the periods of shallow sleep. Stage N3 (NREM 3) is the period of deep sleep.

NREM sleep and REM sleep alternate within sleep cycles of approximately 90 minutes in length. Approximately 4 to 5 NREM/REM cycles occur per night. NREM sleep constitutes about three quarters of each 90-minute cycle and approximately 75-80% of total sleep time in adults. Stage 2 of NREM sleep generally constitutes approximately 45% to 55% of sleep. REM sleep constitutes usually 20-25% of total sleep (Carskadon and Dement 2011).

1.1 Activity of the autonomic nervous system during sleep stages

The regulation of circulatory functions during the wake-sleep cycle is controlled by the autonomic nervous system (ANS).

The transition from wakefulness to NREM sleep is accompanied by increases in parasympathetic-nerve activity (PNA) and reductions in sympathetic-nerve activity (SNA), which together decrease the heart rate and blood pressure (Somers et al. 1993). NREM sleep is a state of lessened metabolic demands and cardiovascular quiescence – PNA is dominant and SNA is lowered and stable. Since adults spend 75-80% of their total sleep time in NREM sleep, sleep is generally considered a time of parasympathetic tone predominance and cardiovascular relaxation.

During the transition from NREM to REM sleep, the state of parasympathetic tone predominance is interrupted. REM sleep is accompanied by neural sympathetic activity similar to that while awake. Major surges in cardiac SNA are concentrated in short, irregular periods and may reach levels higher than during wakefulness (Somers et al. 1993).

During REM sleep, there is a marked increase in both the frequency and height of sympathetic bursts (Fig. 1), associated with intermittent striking surges in heart rate and blood pressure (Somers et al. 1993).

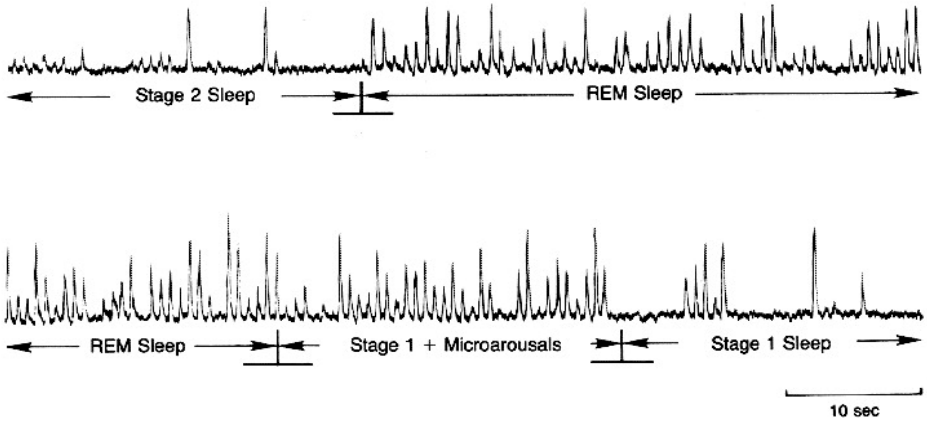

Figure 1. Sympathetic-nerve activity during sleep stages (neurogram). Changes in discharge frequency and amplitude are shown during the transition from stage 2 sleep to REM sleep (upper tracing) and the transition from REM sleep to stage 1 sleep with frequent "microarousals" and then to established stage 1 sleep (lower tracing).
Reproduced with permission from Somers at al. 1993, Copyright Massachusetts Medical Society.

Although, heart rate and blood pressure can increase similar to levels seen during wakefulness (Verrier et al. 1996), the average blood pressure and heart rate remain below waking levels since REM sleep comprises only 20% of total sleep time.

In general, the dynamics of heart rhythm vary between sleep states. The autonomic stability of NREM sleep provides a neurohumoral background during which the heart has an opportunity for relaxation. REM sleep can be described as erratic, it is characterized by a varying pattern of heart rate.

2. OBSTRUCTIVE SLEEP APNEA

Breath-related sleep disorders describe a group of disorders characterized by abnormalities in the frequency and depth of breathing during sleep. It consists of a spectrum of clinical disorders ranging from simple snoring to more serious forms.

Obstructive sleep apnea (OSA) is the most prevalent variant of sleep-disordered breathing. Prevalence varies according to the population studied – the estimated prevalence in men is 3-8% and in women 1-5% (Punjabi 2008). The Wisconsin Sleep Cohort Study of 30-60 year old workers found that 4% of men and 2% of women suffer from this disorder (Young et al. 1993). With progressively rising prevalence, OSA is attributable to the increasingly aged population and the obesity epidemic (Peppard et al. 2013).

The prevalence rates increase with age in both genders, with each 10-year increase in age, the odds ratio of having obstructive sleep apnea is 2.2 (Duran et al. 2001).

2.1 Pathophysiology of obstructive sleep apnea

Obstuctive sleep apnea is characterized by intermittent episodes of partial or complete obstruction (collapse) of the upper airway (pharynx) during sleep (Fig. 2) resulting in reduced (hypopnoea) or absent (apnoea) airflow at the nose/mouth (Deegan and McNicholas 1995).

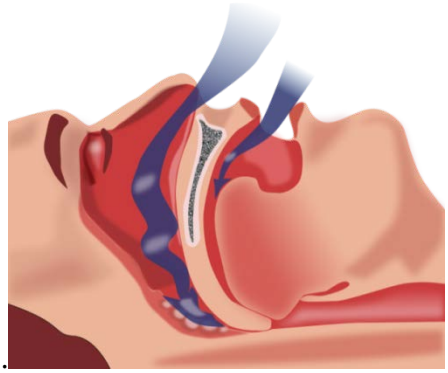

Figure 2. Illustration of the airway obstruction.
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Each episode of airway obstruction is associated with absent or decreased air entry into the lungs. The condition is usually associated with hypoxaemia and apnoeas are typically terminated by brief arousals (microarousals), which result in marked sleep fragmentation (Deegan and McNicholas 1995).

OSA is associated with nocturnal autonomic imbalance, with enhanced parasympathetic tone during the apneas and hypopneas and enhanced SNS activation subsequent to the apneic events (Guilleminault et al. 2005). Hypoxia, as a result of the obstructive apneic episodes, augments sympathetic activity via reflex mechanisms, stimulating peripheral and central chemoreceptors. The increase in SNA by hypoxia is amplified by increases in carbon dioxide levels caused by the apnea (Somers et al. 1989). The SNS activation leads to surges in heart rate and blood pressure, increased myocardial workload and myocardial oxygen demand (Somers et al. 1995; Stoohs and Guilleminault 1992). In addition, it has been indicated that patients with OSA have an increased sympathetic predominance during REM sleep (Somers et al. 1995; Narkiewicz et al. 1998). Airway obstruction is eventually terminated by an arousal from sleep and breathing resumes.

Repeated episodes of absence of air flow are associated with a number of pathophysiological effects that have important clinical consequences. The pattern of intermittent hypoxia seems to be a key pathophysiological cause of adverse cardiovascular effects (Maeder et al. 2016). The adverse effects of OSA on the cardiovascular system are not only related to sleep. The surges in SNA occur repetitively with each obstructive apnea episode leading to the persistent autonomic imbalance. Recurrent hypoxia leads to the heightened sympathetic drive which will continue while the person is awake (Somers et al. 1995).

Compared with healthy controls, patients with OSA have faster heart rates and reduced heart rate variability during sleep and wakefulness (Somers et al. 1995; Narkiewicz et al. 1998), suggesting that there is increased cardiac sympathetic drive.

2.2 Sudden cardiac death and OSA

A growing body of evidence confirms strong associations between OSA and cardiovascular diseases, including coronary artery disease (Lamberts et al. 2014), hypertension (Peppard et al. 2000; Kohler at al. 2011; Vardhan and Shanmuganandan 2012; Luyster et al. 2014) and ventricular dysfunction (Arias et al. 2005; Romero-Corral et al. 2007; Danika et al. 2014; Korcarz et al. 2016).

Obstructive sleep apnea has been associated with the occurrence of different kinds of arrhythmias (Amino et al. 2016). The Sleep Heart Health Study reported that OSA patients had a significantly higher rate of ventricular arrhythmias compared with non-OSA patients. Individuals with OSA had almost twice the odds of complex ventricular ectopy compared with those without OSA (OR, 1.74; 95% CI, 1.11–2.74), even after adjusting for age, sex, body mass index, and coronary artery disease (Mehra et al. 2006).

An increased risk of ventricular arrhythmias, either as a result of nocturnal myocardial ischemia (decreased myocardial oxygen supply) or increased SNA, may account for the increased risk of SCD in OSA patients.

The study of the diurnal timing of SCD demonstrated that patients with OSA were more likely to experience their sudden events at night than those without OSA. In subjects with OSA, the relative risk of SCD from midnight to 6 am was 2.6, compared with the relative risk of 0.8 in non-OSA subjects (Gami et al. 2005). It was suggested that SCD is more likely to occur during usual sleep hours in individuals with OSA, which is the time when SCD is least likely in the general population.

There is some new evidence showing the association of OSA with sudden cardiac death. The longitudinal study, in which 10,701 patients were included and followed for 15 years, revealed that OSA predicted the risk of SCD and the magnitude of risk was predicted by OSA severity (Gami et al. 2013).

Although the exact pathophysiological factors linking OSA and ventricular arrhythmias are not conclusively identified, patients with sleep apnea may be predisposed to arrhythmias because of alterations in sympathetic and parasympathetic nervous system activity occurring with apneas and arousals.

Chronic sleep fragmentation and intermittent hypoxia may shift the sympatho-vagal balance toward sympathetic predominance and a vagal withdrawal (Shepard et al. 1985; Palma et al. 2013) which may predispose to increased myocardial electrical instability.

2.3 Polysomnography (sleep study)

Polysomnography (PSG) is the gold standard for the diagnosis of OSA, according to sleep medicine guidelines (Epstein et al. 2009). The device used for measuring and recording physiological signals during sleep is called as polysomnograph. The test result is called a polysomnogram (Fig. 3). The overnight sleep study is performed in a sleep laboratory, is continuously supervised by a trained technician and scored by a sleep specialist. PSG consists of a simultaneous recording of multiple physiological parameters related to wakefulness and sleep stages.

Current standards for overnight PSG require the concurrent monitoring of sleep structure, cardiac rhythm, oxyhemoglobin saturation, and respiration (Berry et al. 2017). The general parameters that must be reported (Berry et al. 2017):

- electroencephalogram derivations (brain electrical activity);
- electrooculogram derivations (eye movement);
- chin electromyogram (chin muscle activity);
- leg electromyogram (leg muscle activity);
- airflow signals;
- respiratory effort signals (chest and abdominal movement);
- oxygen saturation;
- body position;
- *electrocardiogram* (myocardial electrical activity).

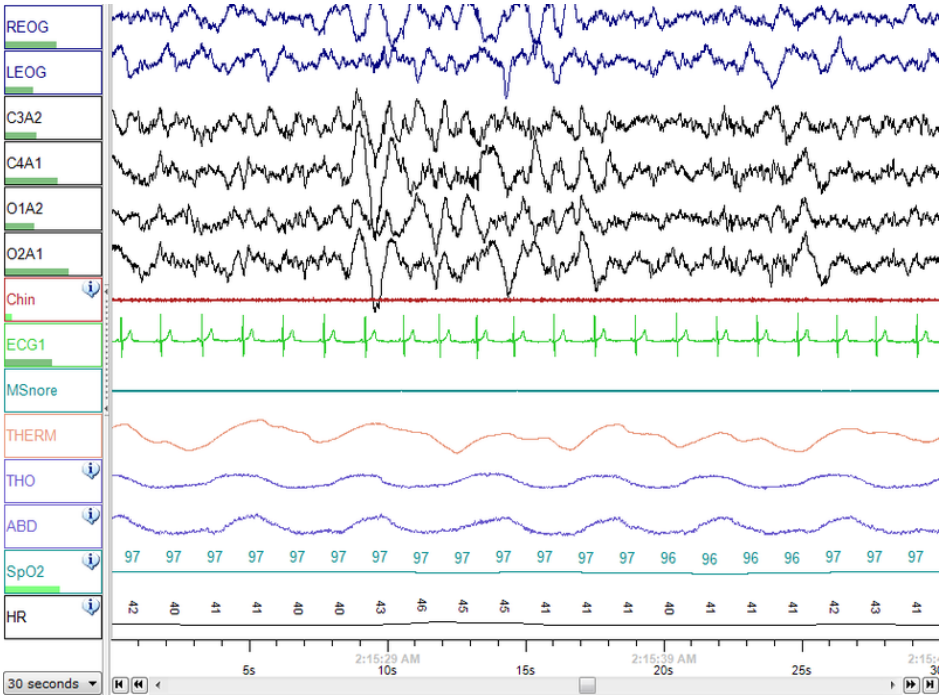

Figure 3. Illustration of the polysomnogram. Screenshot of a person in stage N3 sleep. [CC: By Nascar Ed, https://creativecommons.org/licenses/by-sa/3.0/deed.en].

OSA is diagnosed based on a sleep study where the number of apneas and hypopneas is assessed to calculate the apnea–hypopnea index (AHI). The AHI is defined as the average number of apnea and hypopnea episodes that occur during sleep expressed in events per hour, it is a commonly used clinical index that describes the severity of OSA. OSA severity is commonly defined as mild with an AHI ≥ 5 and < 15, moderate with an AHI ≥ 15 and ≤ 30, or severe with an AHI > 30 (Epstein et al. 2009). An AHI of less than five events per hour of sleep is considered to be normal.

In summary, OSA is a heterogeneous disorder. Increased SNA plays an important role for the development of lethal ventricular arrhythmias and may explain an increased risk of SCD. Polysomnography, also called a sleep study, is a comprehensive recording of the physiological changes that occur during sleep.

3. MEASURES OF VENTRICULAR EPOLARIZATION

Myocardial electrical instability, a predisposition to potentially life-threatening ventricular arrhythmias, can be indirectly assessed by non-invasive parameters, including those reflecting ventricular repolarization variability and prolongation.

A parameter derived from the ECG signals called the QT interval can be used in the evaluation of ventricular repolarization abnormalities. The QT interval (Fig. 4) represents the time from the beginning of ventricular depolarization (beginning of the QRS complex) to the end of ventricular repolarization (end of the T wave).

The selection of lead II for QT measurement, when a single ECG lead is used, is based on the assumption that the vectors of repolarization in that lead result in a long single wave rather than discrete T and U waves (Goldenberg et al. 2006).

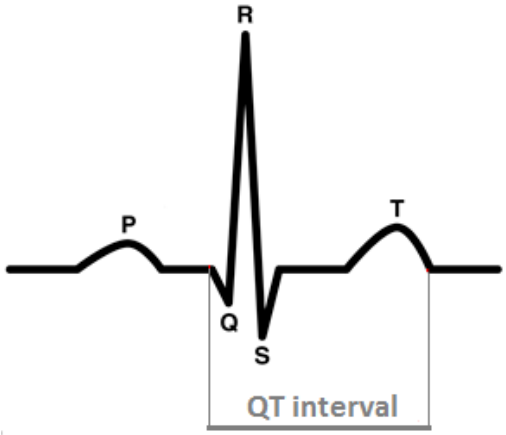

Figure 4. Illustration of the QT interval (ECG).

QT intervals can be measured manually, which is time-consuming; therefore, specific software algorithms for the automated measurement of electrocardiographic durations have been developed (Laguna et al. 1994, Moody et al. 2006).

Different QT interval dispersion, prolongation and variability estimation models have demonstrated their utility for high-risk patient identification. Although ventricular repolarization determination methods have been recognized as powerful predictors of arrhythmic events and SCD in heart disease population (Barr et al. 1994; Periömäki et al. 1995; Berger et al. 1997; Atiga et al. 1998; Dobson et al. 2011; Fischer et al. 2015), only few studies have examined QT interval properties in OSA patients (Gillis et al. 1991; Baumert et al. 2008; Rossi et al. 2012).

In addition, limited data (Lanfranchi et al. 2002) is available concerning QT interval variability and duration changes during various sleep stages.

3.1 QT interval variability – measurement and clinical value

The clinical reliability of QT interval measurement is complicated because of its substantial rate dependence with a lengthening at slow and shortening at fast heart rates (Smetana and Malik 2013). The duration of the QT interval in the ECG may vary also between individual beats, reflecting beat-to-beat changes in ventricular repolarization – QT interval variability (QTV). Under normal conditions, QTV is small, with a standard deviation typically below 5 ms (Avbelj et al. 2003; Baumert et al. 2016).

Although the mechanisms contributing to QTV are incompletely understood, ANS activity and reduced repolarisation reserve (functioning ion channel redundancy that can compensate for damaged channels if necessary) have both been implicated (Cappato et al. 1991; Yeregani et al. 2000a; Magnano et al. 2002; Piccirillo et al. 2009; Baumert et al. 2009; Porta et al. 2010; Baumert et al. 2011).

Beat-to-beat changes in repolarization variability can be quantified using a number of algorithms. QT interval variability is most often measured using the QT variability index (QTVI), proposed by Berger and colleagues (1997). QTVI is a non-invasive measure of QT interval variability that assesses temporal myocardial repolarization lability. The index is defined as:

$$QTVI = \log_{10}\left(\frac{\frac{QTv}{QTm^2}}{\frac{RRv}{RRm^2}}\right), \qquad (1)$$

where QTv represents the QT interval variance, QTm is the mean QT interval, RRv is the RR interval variance, and RRm is the mean RR interval. The index quantifies the magnitude of QT interval variation, normalized by both the mean QT duration and the magnitude of HR variation. The recommended duration of the recording to determine QT variability is 256 s (Berger et al.1997).

To interpret results, it is important to understand that a rise in QTVI could be due to either an increase in QT variance or a fall in HR variance (Berger et al. 1997). Healthy individuals typically have QTVI values less than −1 (Dobson et al. 2013). Decreased QTVI negativity and positive values indicate a propensity for malignant ventricular arrhythmias (Baumert et al. 2016).

QTVI has been utilized as a predictor of malignant ventricular arrhythmias and risk for SCD in various cardiac (Atiga et al. 2000; Vrtovec et al. 2000; Murabayashi et al. 2002; Haigney et al. 2004; Piccirillo et al. 2007; Haigney et al. 2009; Tereshchenko et al. 2012; Niemeijer et al. 2014) and non-cardiac conditions (Alam et al. 2009; Gao et al. 2005; Yeragani et al. 2000b). QTVI is an assessment tool for risk of SCD not only in high-risk groups but also in patients with mild-to-moderate arrhythmic risk (Atiga et al. 1998; Berger et al. 1997). It has been observed that elevation of QT variance, rather than a drop in HR variance, was responsible for increased QTVI in cardiac patients (Tereshchenko et al. 2012). In non-cardiac conditions, decreased HRV and unchanged or mildly increased QT variance was usually observed (Tereshchenko and Berger 2011).

Recently, Baumert and co-authors (2016) published the position statement and consensus guidance on measurement, physiological basis, and clinical value of QT interval variability in body surface ECG. In that paper, the QT variability index was considered as an important high risk patient stratification method.

Limited data is available on QTVI as a parameter predicting ventricular arrhythmias in sleep-related breathing disorders. Baumert et al. (2008) evaluated OSA-related changes in variability of QT interval duration and heart rate and the relationship of these parameters to disease severity. Their study suggested that beat-to-beat QT interval analysis might be more sensitive than standard HRV parameters. However, the study did not evaluate gender differences.

3.2 Corrected QT interval – measurement and clinical value

The normal QT interval varies with time of the day and with heart rate (Molnar et al. 1996; Goldberger et al. 2008). Therefore, the QT interval should undergo rate correction (QTc) to compare measurements at different time points and at different heart rates (Vandenberk et al. 2016).

Several mathematical algorithms have been proposed to describe the QT interval and heart rate (QT/RR) relationship and to derive a heart rate-corrected QT interval (i.e., a HR independent QT interval). Some of the algorithms for calculating QTc are shown in Table 1.

Heart rate correction methods assume that a mathematical form exists to describe the physiological QT/RR relation (Malik et al. 2002).

One of the earliest formulas was published by Bazett (1920). It is the most used correction method in clinical studies, in spite of the fact that it overcorrects the QT interval at high heart rates and under-corrects it at slow heart rates (Rautaharju et al. 1990; Dogan et al. 2005). Therefore, Bazett's formula can only be applied to correct the QT interval within a range of heart rate between 50 and 90 beats per minute. The formula defines the normal value as < 440 ms for men and < 460 ms for women (Bazett 1920).

Table 1. Algorithms for calculating QTc

Denomination	***Formula***
Exponential formula (Bazett, 1920)	$QTc = QT / RR^{0.5}$
Exponential formula (Fridericia, 1920)	$QTc = QT / RR^{0,33}$
Linear formula (Sagie et al. 1992)	$QTc = QT + 0,154\ (1 - RR)$
Linear model (Malik et al. 2002)	$QTc = QT + \alpha \times (1 - RR)$
Hyperbolic model (Malik et al. 2002)	$QTc = QT + \alpha \times (1 / RR - 1)$
Parabolic model (Malik et al. 2002)	$QTc = QT/RR^{a}$
Logarithmic model (Malik et al. 2002)	$QTc = QT - \alpha \times \log (RR)$
Modified logarithmic model (Malik et al. 2002)	$QTc = \log (e^{QT} + \alpha \times (1 - RR))$
Exponential model (Malik et al. 2002)	$QTc = QT + \alpha \times (e^{-RR} - 1/e)$

Abbreviations: QTc, corrected QT interval; QT, QT interval; α, slope of the regression; RR, RR interval; e, exponential function with base.

The American Heart Association, the American College of Cardiology Foundation, and the Heart Rhythm Society (AHA/ACCF/HRS) have recommended that rate correction of the QT interval should not be attempted when the heart rate variability is large (Rautaharju et al. 2009). In addition, there is still no definite consensus about the normal limits of the QTc interval (Molnar et al. 1996; Toivonen 2002).

A heart rate correction formula that performs well in one subject may overcorrect or undercorrect the QT interval in another subject (Malik et al. 2002). Since QT/RR relationship varies among individuals, individual-specific correction formulas that take into account hysteresis (the time of adaptation of the QT interval to HR) effects have been proposed (Malik et al. 2013).

Several studies have associated the QTc interval with the risk of both arrhythmias and SCD in the general population (Schouten et al. 1991; Montanez et al. 2004; Straus et al. 2006; Zhang et al. 2011) and in patients with cardiovascular disease (Algra et al. 1991; Malik et al. 2010).

The data on increased QTc in OSA is rather inconclusive. Prolongation of the QT interval in OSA patients has been reported (Çiçek et al. 2012; Shamsuzzaman et al. 2015).

Gillis and colleagues (1991) found that apneic episodes in OSA were associated with both QT prolongation due to increased vagal activity and abrupt QT shortening during post-apnea due to increased sympathetic tone and/or vagal withdrawal; and yet, Barta et al. (2010) studying the effect of sleep apnea demonstrated that QTc interval did not show any significant change in 24-hours.

3.3 Tp-e – measurement and clinical value

The T peak-to-end (Tp-e) interval represents a ECG index of arrhythmia risk (Kors et al. 2008). It has been suggested that prolongation of the Tp-e interval reflects global (apico-basal) heterogeneity of ventricular repolarization and can be used as a marker for risk of ventricular arrhythmias.

Increased Tp-e interval has been reported to be associated with cardiac diseases (Haarmark et al. 2009), potentially life-threatening ventricular arrhythmias and SCD (Panikkath et al. 2011), as well as in patients with moderate to severe OSA (Kilicaslan et al. 2012).

3.4 Electrophysiological effects of normal sleep and gender

Studies investigating the effect of sleep on the QT interval have established that QT interval duration exhibits a circadian pattern (Extramiana et al. 1999). Browne et al. (1983) first reported a prolongation of the QT interval during the night. In normal subjects, QTV appears to be lower during night time compared with day time (Kostis and Belina 2000; Bonnemeier et al. 2003; Jensen et al. 2004). Diurnal changes of the QT interval are dependent on variations in autonomic tone (Bexton et al. 1986; Murakawa et al. 1992).

Gender is an important modulating factor of ventricular repolarization. Females have longer action potentials, a lower repolarization reserve (Somerts et al. 1993; Surawicz and Parikh 2003; Abi-Gerges et al. 2004; Sredniawa et al. 2005; Rautaharju et al. 2014), and higher susceptibility to several arrhythmias than the same-aged males (Yarnoz and Curtis 2008). The first to confirm the gender difference was Bazett (1920), who showed a 24ms longer QT interval in females than in males. Recent studies have also shown a gender effect on QT variability – increased QTV in females (Hasan et al. 2012; Hnatkova et al. 2013; Sur et al. 2013).

It is considered that autonomic nervous function differences and hormonal influence on ion-channels´ function are among the responsible mechanisms for gender differences in ventricular repolarization and corresponding arrhythmic risk (Piccirillo et al. 2009; Baumert et al. 2016). Nevertheless, there is little evidence addressing the association between the ventricular repolarization parameters and sleep stages (Gillis et al. 1988, Lanfranchi et al. 2002; Baumert et al. 2008).

In summary, there is a growing clinical interest in assessing repolarization instability from surface ECGs. QTVI has been proposed as a possible non-invasive assessment tool for identifying patients at risk of SCD. QT prolongation is associated with a risk for cardiac arrhythmias. The purpose of heart rate correction is to receive QTc value independent of the underlying HR. Little is known about the proper use of QT interval parameters in clinical practice for evaluation of risk in patients with OSA and the QT interval changes in female and male patients during various sleep stages.

4. EXPERIMENTAL STUDIES

4.1 Methods

All studies were performed after approval by the Tallinn Medical Research Ethics Committee at the National Institute for Health Development, decision no. 1170 (30.09.2015). The studies involved the retrospective analysis of laboratory-based PSG recordings by using the patient database of the Mae Pindmaa Sleep Clinic (Tallinn, Estonia). The database contains data from 396 (220 male and 176 female) patients.

Study population

The initial study population consisted of 179 (106 male and 73 female) patients, 20 to 80 years, referred to the Mae Pindmaa Sleep Clinic (Tallinn, Estonia) between 2013 and 2014 for a sleep study because of clinically suspected breathing-related sleep disorders. Patients were selected on the basis of stored PSG recordings and clinical characteristics. The flow chart of the study subjects selection is shown in Figure 5.

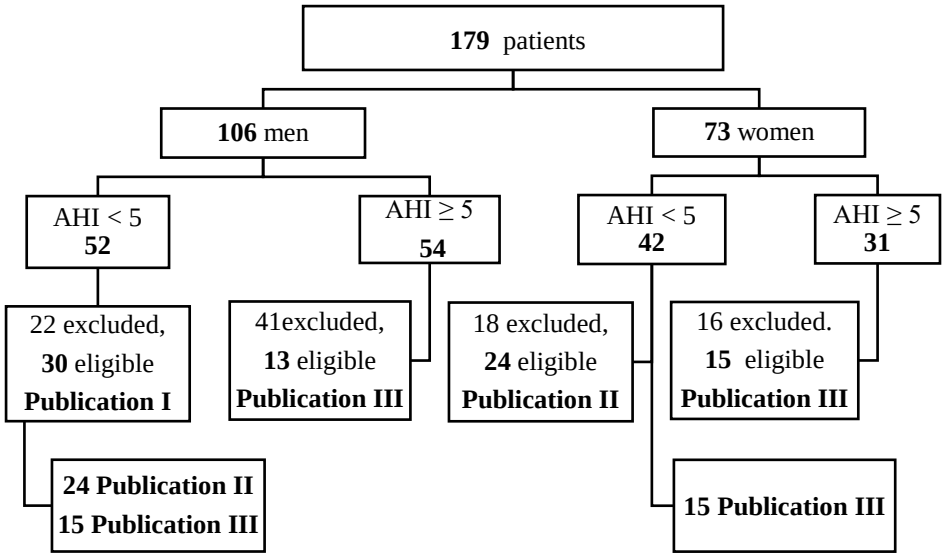

Figure 5. Flow chart of study population. Abbreviations: AHI, apnea-hypopnea index.

In all experiments, the following exclusion criteria were applied: evidence of cardiac, pulmonary or central nervous system disease; use of medications known to affect the QT interval parameters (e.g. I and III class antiarrhythmic, antihistaminic, psychotropic, or antibiotic drugs); abnormal ECG (e.g. non-sinus rhythm, intraventricular conduction delay); poor ECG signal quality; insufficient length of analyzable sleep stage.

After the exclusion criteria were applied, 82 patients were selected from the initial study population. The number of patients in the studies was as follows:

- 30 male patients in the first study (Publication I);
- 48 (24 male and 24 female) patients in the second study (Publication II);
- 58 (28 male and 30 female) patients in the third study (Publication III).

It is important to point out that for the second study, male patients were selected from the first study population and for the third study, the non-OSA group (males and females) was selected from subjects of the second study (Figure 5).

Polysomnographic recordings analysis

The PSG data was obtained from routine diagnostic procedures. The signals were registered with polysomnography recorder Rembrandt Monet Artist SLP EZ 24 (Medicare Automation B.V, Netherlands). Electrodes and sensors were placed by a professional polysomnography nurse. Sampling frequency for physiological signals was 200 Hz. The duration of the recordings was from 8 to 9 hours. Data processing was performed using the Rembrandt Analysis Manager (version 7.5, Medicare Automation B.V, the Netherlands). All PSG recordings were analyzed by a certified sleep technician and verified by a sleep physician according to the American Academy of Sleep Medicine criteria (Iber et al. 2007).

The selection of digital PSG recordings for the research study (Publications I – III) was carried out in the Department of Health Technologies at the Tallinn University of Technology. In each recording, two awake, three REM and three NREM (stage 2) sleep episodes (300 consecutive seconds each) suitable for further processing were selected. For Publication II an additional episode of NREM stage 3 was included for each patient. All selected epochs were marked for further usage in the analysis.

ECG signal pre-processing and analysis

ECG signals (lead II) from the selected episodes of polysomnograms were anonymized, converted to EDF format and resampled to sampling frequency of 256 Hz (Publication I) and 512 Hz (Publication II and III).

The recorded signals were pre-processed in LabVIEW (National Instruments, USA) environment, applying the signal converting Physionet toolkit (Goldberger et al. 2000).

The R-wave peaks were detected and the extrasystoles identified using Pan-Tompkins algorithm (Hamilton and Tompkins 1986). The RR intervals were converted to Normal-to-Normal intervals. Ectopic beats, as well as pre-and post-extrasystolic beats, were not included in the analysis.

The T-wave location and type were detected using Ecgpuwave software (Laguna et al. 1994). Only monophasic well-defined T-waves were accepted.

The end of T- wave was determined by the tangent method (Lepeschkine and Surawicz 1952; Batchvarov et al. 1998) (Fig. 6).

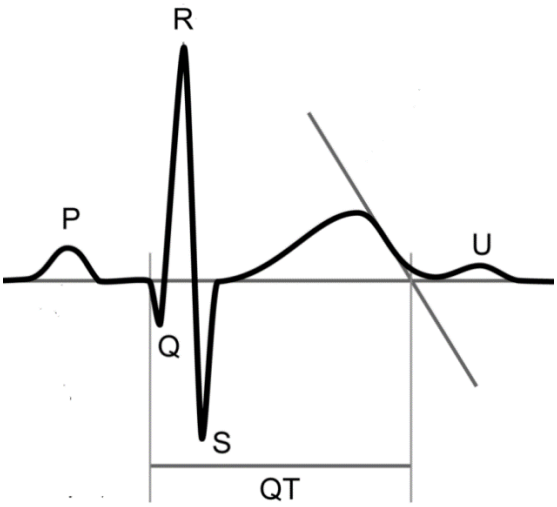

Figure 6. The tangent method. The end of the T wave is determined by the intersection of a tangent line extrapolated from the T wave at the point of maximum downslope to the isoelectric baseline.

The inter-observer measurement error was avoided by using measurements made by the same trained operator.

Publications I – III present the algorithms used in the experimental studies. The QT interval variability index (Berger et al. 1997) was used to measure QT interval variability (Formula 1: 19).

The average absolute QT was normalized for variations of RR by applying correction algorithms as follows:

nonlinear formula (Bazett 1920)

$$QTc = \frac{QT}{RR^{0.5}}, \tag{2}$$

linear regression model (Malik et al. 2002)

$$QTc = QT + \alpha \cdot (1 - RR), \tag{3}$$

and parabolic regression model (Malik et al. 2002)

$$QTc = \frac{QT}{RR^{\alpha}}, \tag{4}$$

where α is the slope of the regression.

The rationale for choosing specifically these three heart correction methods are as follows:

- *Bazett's formula* – commonly used in clinical practice, can be applied to correct the QT interval within a range of heart rate between 50 and 90 beats per minute (Rautaharju et al. 1990; Rautaharju et al. 2009);
- *Linear and parabolic regression models* – to determine a precise determination of QTc interval, individually optimized HR correction is more sensitive than an universal correction formula to detect minor changes in QTc interval (Malik et al. 2002), linear and parabolic regression models are the types of optimum models (Malik et al. 2002; Veski et al. 2010);
- *α minimal and α 0.2* – to provide more accurate results for heart rate correction (Malik et al. 2002; Veski et al. 2010).

In addition, the T-wave apex to T-wave end interval (Tp-e) duration in all episodes was measured (Publication I).

Statistical analysis

In Publications I – III, the results were presented as means ± standard deviation (SD). Statistical tests used in all experiments are presented in Table 2.

Table 2. Summary of statistical tests

Publication	Statistical tests
I	*Student's t-test* – Between-group comparisons of variables.
II	*Kolmogorov-Smirnov test* – Normality of study variables.
	Student's t-test – Study population characteristics and sleep variables between genders, difference between sleep stages within gender.
	Wilcoxon rank sum test – Non-normally distributed AHI.
	Two-way analysis of variance followed by Tukey HSD post-hoc tests for pairwise comparisons – Differences between wake-sleep stages and genders.
III	*Kolmogorov-Smirnov test* – Normality of study variables.
	Student's t-test – Study subjects characteristics, sleep variables.
	Wilcoxon rank sum test – Non-normally distributed AHI.
	Full factorial three-way analysis of variance followed by Tukey HSD post-hoc tests for pairwise comparisons – HRV, QTV interval variability and duration differences between OSA and non-OSA groups, wake-sleep stages and genders.

Abbreviations: AHI, apnea-hypopnea index; HRV, heart rate variability; OSA, obstructive sleep apnea.

For the statistical analysis the Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA) (Publication I – III) and statistical package R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) (Publication II – III) were used. Two-sided p value lower than 0.05 was considered statistically significant.

4.2 Results

General characteristics of the study population are summarized in Table 3.

Table 3. Characteristics of study subjects

	Publication I	**Publication II**	**Publication III**
Total number of patients (M/F)	30 (M)	48 (24/24)	58 (28/30) OSA: 28 (13/15) non-OSA: 30 (15/15)
Age (yr)	40.0 ± 11.5	M: 40.0 ± 11.9 F: 43.4 ± 15.2	OSA/M: 47.5 ± 11.7 OSA/F: 60.0 ± 9.4 non-OSA/M: 39.2 ± 12.1 non-OSA/F: 51.5 ± 12.4
BMI (kg/m²)	26.8 ± 4.8 kg/m²	M: 26.1 ± 4.2 F: 24.7 ± 4.1	OSA/M: 32.5 ± 2.7 OSA/F: 33.2 ± 6.1 non-OSA/M: 26.0 ± 4.1 non-OSA/F: 25.5 ± 2.9
AHI (n/h)	1.5 ± 1.4	M: 1.4 ± 1.4 F: 0.9 ± 1.1	OSA/M: 31.2 ± 18.1 OSA/F: 19.7 ± 19.8 non-OSA/M: 1.2 ± 1.0 non-OSA/F: 1.0 ± 1.2
SpO_2 (%)	Awake 94.8 ± 1.9 NREM 94.5 ± 1.3 REM 94.6 ± 1.6	M: 95.0 ± 1.5 F: 96.0 ± 1.2	OSA/M: 90.9 ± 7.8 OSA/F: 92.4 ± 1.4 non-OSA/M: 95.4 ± 0.9 non-OSA/F: 95.3 ± 1.4

Abbreviations: M, males; F, females; OSA, obstructive sleep apnea; NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage; BMI, body mass index; AHI, apnea-hypopnea index; SpO_2, arterial oxyhemoglobin saturation.

In Publication II, there were no significant group differences in general characteristics. In Publication III, there were no significant differences between OSA and non-OSA males in terms of the mean age but females with OSA were older than females without OSA ($P = 0.026$). As expected, patients with OSA had a higher BMI, AHI and lower SpO_2 when compared with patients without OSA. Sleep structure was similar in all groups, including total sleep time, percentage of NREM and REM sleep (Publication I – III).

4.2.1 REM sleep and ventricular repolarization (Publication I)

Mean values of QT interval variability and duration during the sleep stages in non-apneic males are presented in Table 4.

Table 4. Mean values of QT interval variability and duration calculated by mathematical algorithms in wake-sleep stages.

Variables	Awake	NREM	REM
QTVI	–1.0 ± 0.3	–1.1 ± 0.3	–1.2 ± 0.3
Tp-e (ms)	72.4 ± 7.2	75.9 ± 6.6	74.3 ± 6.4
QTc Bazett mean (ms)	383.7 ± 18.4	384.7 ± 19.9	388.8 ± 19.9
QTc Lin α min mean (ms)	376.2 ± 22.1	389.7 ± 21.7	384.2 ± 21.6
QTc Par α min mean (ms)	376.0 ± 22.3	389.6 ± 21.7	384.1 ± 21.7
QTc Lin α 0.2 mean (ms)	374.5 ± 24.6	389.3 ± 23.0	382.0 ± 23.8
QTc Par α 0.2 mean (ms)	377.9 ± 18.6	387.3 ± 18.9	384.5 ± 19.8

Data is expressed as means ± SD. Abbreviations: NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage; QTVI, QT variability index; Tpe, T-wave peak to T-wave end interval; QTc Bazett, rate corrected QT interval based on Bazett's formula; QTc Lin α min, rate corrected QT interval based on linear regression model α minimum; QTc Par α min, rate corrected QT interval based on parabolic regression model α minimum; QTc Lin α 0.2, rate corrected QT interval based on linear regression model α 0.2; QTc Par α 0.2, rate corrected QT interval based on parabolic regression model α 0.2.

Mean QTVI values were similar to those of healthy controls (–1.29 ± 0.51) reported by Berger et al. (1997).

The findings demonstrated that no statistically significant difference in the mean values of QTVI, Tp-e, and QTc was found when REM sleep was compared to the wake stage or NREM sleep ($P > 0.05$).

4.2.2 Gender and ventricular repolarization (Publication II)

In male subjects, mean values of QTVI while awake, in NREM and REM sleep were –1.1 ± 0.2, –1.1 ± 0.3, –1.3 ± 0.2; in female subjects, the mean values of QTVI were –0.9 ± 0.4, –0.9 ± 0.4, and –1.1 ± 0.3, respectively.

QT variability index distributions for male and female patients are demonstrated in Figure 7.

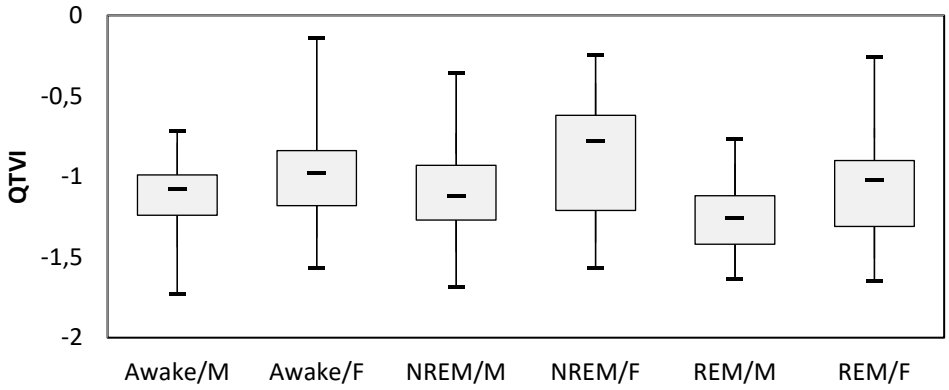

Figure 7. QT variability index distributions. Abbreviations: M, males; F, females; QTVI, QT variability index; NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage.

A gender dependent difference in the QTVI mean values in different sleep stages was detected. Females demonstrated more positive QTVI mean values in all wake-sleep stages ($P < 0.05$). At the same time, within genders, no statistically significant difference in the QTVI mean values was found between sleep stages. Also, there were significant differences in the corrected QT interval values between male and female patients in all wake-sleep stages ($P < 0.05$), except between values assessed by the linear regression model with the value of α 0.2.

4.2.3 Electrical remodeling in OSA patients (Publication III)

The mean QTVI was statistically greater (more positive) in OSA patients than in non-OSA patients for males while awake (Figure 8). In females, the mean QTVI was statistically greater in OSA patients than in non-OSA patients in all sleep stages (Figure 9).

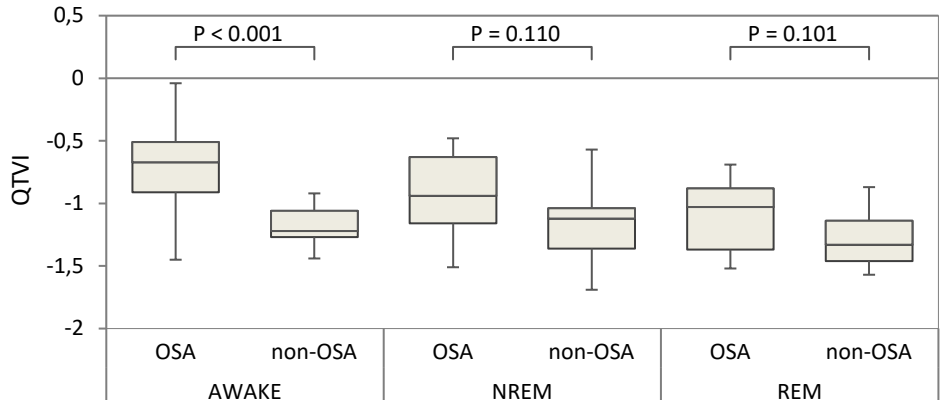

Figure 8. QT variability index distributions for male patients. Abbreviations: QTVI, QT variability index; NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage; OSA, obstructive sleep apnea; non-OSA, without obstructive sleep apnea.

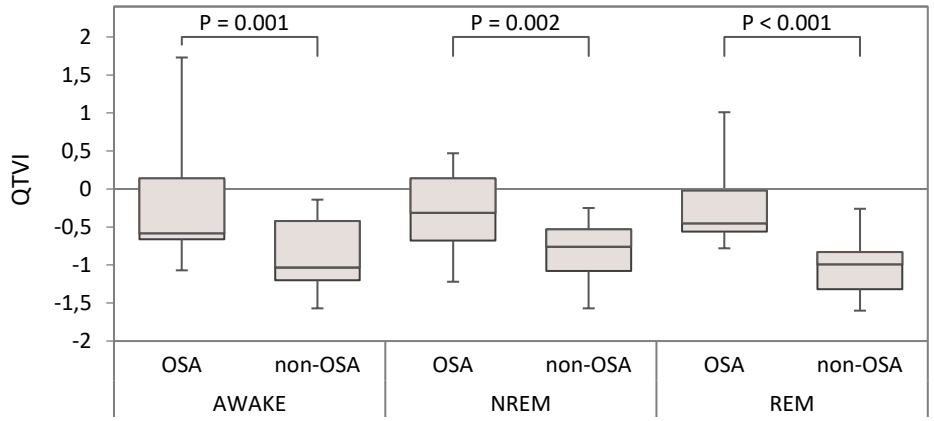

Figure 9. QT variability index distributions for female patients. Abbreviations: QTVI, QT variability index; NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage; OSA, obstructive sleep apnea; non-OSA, without obstructive sleep apnea.

The median and inter quartile range of SDNN (reflecting the overall HRV) and SDQT (reflecting QT variability without normalization to HR) are demonstrated for males in Figure 10. The median and inter quartile range of SDNN and SDQT are demonstrated for females in Figure 11.

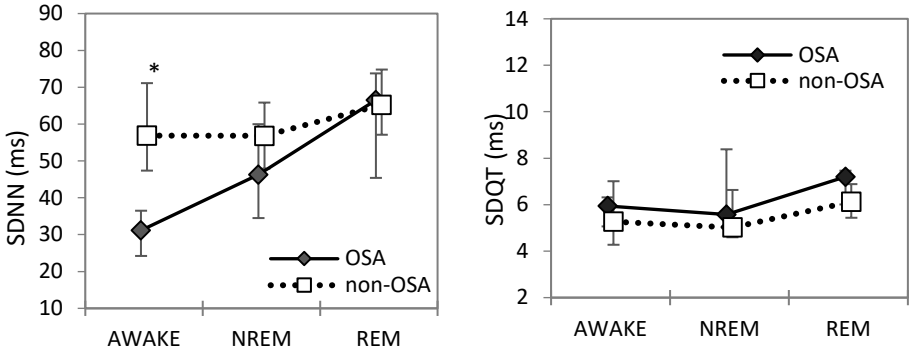

Figure 10. Median and inter quartile range of NN interval (SDNN) and QT interval (SDQT) in male patients with and without OSA in the wake stage, NREM and REM sleep. Stars denote statistically significant ($P < 0.05$) differences between OSA and non-OSA patients.

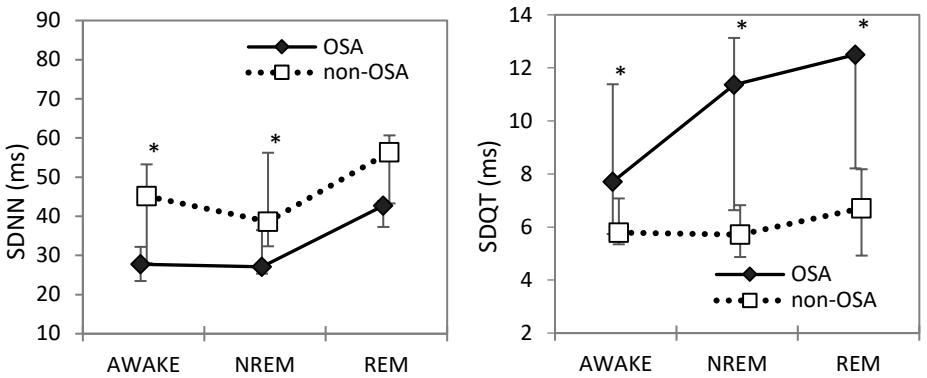

Figure 11. Median and inter quartile range of NN interval (SDNN) and QT interval (SDQT) in female patients with and without OSA in the wake stage, NREM and REM sleep. Stars denote statistically significant ($P < 0.05$) differences between OSA and non-OSA patients.

A comparison of OSA and non-OSA patients revealed no significant differences in the QT interval mean values corrected by any algorithms ($P > 0.05$).

4.3 Discussion

QT interval beat-to-beat variability is influenced by multiple factors. Although the mechanisms contributing to variability are not completely understood, elevated sympathetic activity has been considered to be one of the most important among them (Piccirillo et al. 2009; Baumert et al. 2011).

Therefore, it is tempting to presume that sympathetic bursts in REM sleep have influence on ventricular repolarization temporal lability.

However, the results of the first study (Publication I) indicate that physiological surges (signal inputs) in SNA characterizing REM sleep do not lead to clinically significant fluctuations in beat-to-beat dynamicity of ventricular repolarization. It seems that in the absence of substantial structural and electrical remodeling of myocardium, physiological elevation in sympathetic activity during REM sleep remains subthreshold for clinically significant increase of myocardial electrical instability. This finding is consistent with the opinion that temporal fluctuations in repolarization are aroused by elevated cardiac sympathetic activation in certain pathological conditions only (Baumert et al. 2016). The absence of difference in the mean QTc interval values between NREM and REM stages, calculated by all algorithms (Publication I), confirms the conclusion that sympathetic surges during the physiological REM stage do not adversely affect repolarization.

Accumulating evidence suggests that autonomic nervous function differences and hormonal influence on ion-channels´ function are among the responsible mechanisms for gender differences in ventricular repolarization and corresponding arrhythmic risk (Baumert et al. 2016).

In the second study (Publication II), a gender dependent difference in the QTVI mean values during all sleep stages was detected, females had more positive QTVI values in all wake-sleep stages in comparison to men; despite this, the parameter remained within the normal range in both genders.

The rate-corrected QT interval has been found to be longer in women compared to men (Batchvarov et al. 1998; Abi-Gerges et al. 2004; Rautaharju et al. 2014). The second study (Publication II) demonstrated that when comparing genders, there were significant differences in the corrected QT interval, females had longer QTc intervals than males in every wake-sleep stage.

The results of the third study (Publication III) are generally in line with previous data by Baumert et al. (2008). Even though their study was comprised of 12 males and 8 females, the evaluation of gender differences was not performed. Because of that, the third study (Publication III) was designed to investigate also gender differences in the wake stage and in sleep stages. The results of Publication III demonstrated that OSA was associated with changes in QT interval variability and females with sleep apnea had more positive values of QT variability than males.

Previous data on increased QTc in obstructive sleep apnea is rather inconclusive. Prolonged QT interval in OSA patients has been reported (Çiçek et al. 2012). Rossi et al. (2012) found in a randomized trial that in patients with moderate to severe OSA, two weeks of continuous airway pressure (CPAP) withdrawal led to significant prolonging of QTc. Shamsuzzman et al. (2015) showed that OSA in either men or women was associated with a significant increase in resting daytime QTc. Barta et al. (2010) studying the effect of sleep apnea demonstrated that nocturnal QTc interval did not show any significant change in 24 hours.

The results of the third study (Publication III) are based on the simultaneous application of ventricular repolarization variability and duration assessment algorithms to polysomnographic ECG recordings at wake-sleep stages. The absence of difference of the mean QTc interval values between OSA and non-OSA patients, calculated by all formulas, confirms the conclusion that QTVI is a more valuable prognostic measurement for risk stratification in OSA patients than QTc.

4.4 Epilogue

Beat-to-beat QT interval variability has been investigated in a variety of clinical conditions. Thus, the possibility of assessing OSA influence at the ventricular level has an obvious purpose. Development of methods that identify risk groups is a way to decrease the number of SCD. The major finding of this study is that QTVI is a more useful measurement to detect ventricular repolarization abnormality in OSA patients than measures of QTc. The algorithm for quantifying beat-to-beat fluctuations can be applied to routinely registered polysomnographic ECG recordings in patients with OSA for complementary risk analysis. However, clinical judgment ultimately must be used in deciding which patients need further evaluation. Also, gender-specific cut-off values of QTVI need to be defined before this index can become an integral part of decision-making.

CONCLUSIONS

The novelty of the experimental study reported in this thesis lies in its methodological approach – the simultaneous application of the QT variability index (QTVI) and selected QT interval correction (QTc) algorithms to polysomnographic ECG recordings at various sleep stages.

The main results and implications of the current research were as follows:

1. The results of this study show that REM-sleep related physiological elevation in sympathetic activity does not have an adverse effect on ventricular repolarization. Therefore, increased QT interval variability measured with mathematical algorithms in patients with OSA is a marker for disease-related myocardial electrical instability.
2. Analysis of geneder differences in the absolute mean values of QTVI and QTc during wake-sleep stages confirm that gender is a modulating factor of ventricular repolarization. While comparing the values of QT interval variability index with suggested normal QTVI values, it is important to consider that females tend to have more positive QTVI values than men do.
3. In male and female patients with obstructive sleep apnea, the QT interval variability index (QTVI), calculated by Berger's formula, is a more useful noninvasive quantitative measure of ectrocardiography to detect the electrical instability than measures of QTc.
4. In accordance to the study findings, in males with OSA, decreased NN variability (SDNN, the denominator in the formula) was the cause of the QTVI elevation. In females with OSA, increased QT variance (SDQT, the numerator in the formula), rather than a drop in heart rate variance, was responsible for increased QTVI. Therefore, the interpretation of QTVI in OSA patients needs to reflect the numerator and the denominator.

Finally, the results of this doctoral study offer for researchers and clinicians more insights into the effects of sleep stages on left ventricular myocardial repolarization signals. The QTVI is feasible as a computerized screening tool for detecting abnormalities in cardiac repolarization in patients with OSA. The index can be applied to routinely registered polysomnographic ECG recordings in patients with OSA for complementary risk analysis. Appropriate referral to further cardiac evaluation for malignant arrhythmia may ensure an effective disease management strategy and prevent sudden death. However, prospective trials are needed to prove its prognostic value in OSA patients. Since the magnitude of beat-to-beat QT interval variability varies between genders during wake-sleep stages, the QT variability index should be analysed and interpreted in males and females separately both in research studies and in clinical settings.

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Dedication

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ABSTRACT

Analysis of Ventricular Repolarization Signals in Obstructive Sleep Apnea

In recent decades, the interest in obstructive sleep apnea has grown in the medical and research community due to its established association with ventricular arrhythmias and sudden cardiac death.

The general aim of this research was to investigate the ability of various mathematical algorithms to detect myocardial electrical instability in patients with and without obstructive sleep apnea by analysing polysomnographic recordings. For this purpose, the QT variability index, three QT interval correction methods (two of them with different α-values), and the Tpeak–Tend interval were applied in different sleep stages.

In the first part of the thesis, the physiology of sleep, pathophysiology of obstructive sleep apnea, and measurement principles of electrocardiographic QT interval parameters are discussed. In the second part of the thesis, methods and results of the experimental studies are presented. The first study aimed to determine whether REM sleep affects QT interval variability and duration. The second study was aimed to evaluate the gender effects on the QT interval parameters during different sleep stages. The aim of the third study was to determine which noninvasive quantitative measure can detect myocardial electrical instability in patients with obstructive sleep apnea.

The main findings of this research include:

- The results of this study show that REM-sleep related physiological elevation in sympathetic activity does not have an adverse effect on ventricular repolarization. Therefore, increased QT interval variability in patients with OSA is a marker for disease-related myocardial electrical instability.
- Analysis of geneder differences in the absolute mean values of QTVI and QTc during wake-sleep stages confirm that gender is a modulating factor of ventricular repolarization. While comparing the values of QT interval variability index with suggested normal QTVI values, it is important to consider that females tend to have more positive QTVI values than men do.
- In male and female patients with sleep apnea, the QT interval variability index is a more useful noninvasive quantitative measure of ectrocardiography to detect the electrical instability than QT correction formulas.
- The interpretation of the QTVI values in OSA patients needs to take into account how the numerator (SDQT) and/or the denominator (SDNN) influenced the end result.

The QT variability index is feasible as a computerized screening tool for detecting abnormalities in cardiac repolarization in patients with OSA.

KOKKUVÕTE

Ventrikulaarse repolarisatsiooni signaalide analüüs obstruktiivse uneapnoe korral

Viimastel aastakümnetel on meditsiini- ja teadusringkonnas kasvanud huvi obstruktiivse uneapnoe vastu, mis on tingitud selle haiguse seotusest ventrikulaarsete rütmihäirete ja südame äkksurmaga.

Käesoleva uurimistöö põhieesmärgiks oli uurida valitud polüsomnograafiliste salvestuste põhjal erinevate matemaatiliste algoritmide võimet tuvastada müokardiaalset elektrilist ebastabiilsust obstruktiivse uneapnoega ja apnoeta patsientidel. Sellel eesmärgil kasutati une eri faasides QT intervalli varieeruvuse indeksit, QT-intervalli korrigeerimise valemeid (kahte valemit erinevate α väärtustega) ja Tp-e intervalli.

Töö esimeses osas on käsitletud une füsioloogiat, obstruktiivse uneapnoe patofüsioloogiat ning elektrokardiograafilise QT intervalli parameetrite mõõtmispõhimõtteid. Töö teises osas on käsitletud läbiviidud eksperimentaalsete uuringute meetodikat ja tulemusi. Esimese uuringu eesmärk oli uurida REM unefaasi mõju QT-intervalli varieeruvusele ja kestusele. Teise uuringu eesmärk oli hinnata soolist mõju QT-intervalli parameetritele erinevates unefaasides. Kolmanda uuringu eesmärk oli kindlaks teha, milline kvantitatiivne mõõtmisviis tuvastab obstruktiivse uneapnoeaga patsientidel müokardiaalse elektrilise ebastabiilsuse.

Uurimistöö peamised tulemused on järgmised:

- REM-uni ei avalda kõrvalmõju ventrikulaarsele repolarisatsioonile, mistõttu peab uneapnoe patsientidel matemaatiliste algoritmidega tuvastatud QT-intervalli varieeruvuse suurenemist käsitlema haigusest tingitud müokardi elektrilise ebastabiilsuse näitajana.
- QTVI ja QTc keskmiste väärtuste võrdlus meeste ja naiste seas eri une faasides kinnitab, et soolisus on oluline ventrikulaarset repolarisatsiooni moduleeriv tegur. QTVI väärtuste võrdlemisel normi väärtustega on oluline arvestada, et naistel on QTVI väärtused positiivsemad kui meestel.
- Obstruktiivse uneapnoega mees- ja naispatsientidel on müokardi elektrilise ebastabiilsuse hindamiseks arvutatud QT-intervalli varieeruvuse indeks informatiivsem kui valemitega korrigeeritud QT intervall.
- Obstruktiivse uneapnoe patsientidel QTVI valemiga arvutatud tulemuste interpreteerimisel peab arvestama, kuidas lugeja (SDQT) ja/või nimetaja (SDNN) mõjutas lõpptulemust.

QT intervalli varieeruvuse indeks on arvutipõhine skriinimise vahend, mida on võimalik rakendada kliinilises praktikas uneapnoega patsientidel südame elektrilise ebastabiilsuse hindamiseks.

APPENDIX 1

PUBLICATIONS

Publication I

Viigimae, **M**., Karai, D., Pirn, P., Pilt, K., Meigas, K., Kaik, J. (2015). QT Interval Variability Index and QT Interval Duration in Different Sleep Stages: Analysis of Polysomnographic Recordings in Nonapneic Male Patients. – *Biomed Res Int*, vol 2015, ID 963028. (DOI: 10.1155/2015/963028)

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Research Article

QT Interval Variability Index and QT Interval Duration in Different Sleep Stages: Analysis of Polysomnographic Recordings in Nonapneic Male Patients

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The aim of the study was to determine whether different sleep stages, especially REM sleep, affect QT interval duration and variability in male patients without obstructive sleep apnea (OSA). Polysomnographic recordings of 30 patients were analyzed. Beat-to-beat QT interval variability was calculated using QTV index (QTVI) formula. For QTc interval calculation, in addition to Bazett's formula, linear and parabolic heart rate correction formulas with two separate α values were used. QTVI and QTc values were calculated as means of 2 awake, 3 NREM, and 3 REM sleep episodes; the duration of each episode was 300 sec. Mean QTVI values were not statistically different between sleep stages. Therefore, elevated QTVI values found in patients with OSA cannot be interpreted as physiological sympathetic impact during REM sleep and should be considered as a risk factor for potentially life-threatening ventricular arrhythmias. The absence of difference of the mean QTc interval values between NREM and REM stages seems to confirm our conclusion that sympathetic surges during REM stage do not induce repolarization variability. In patients without notable structural and electrical remodeling of myocardium, physiological elevation in sympathetic activity during REM sleep remains subthreshold concerning clinically significant increase of myocardial electrical instability.

1. Introduction

Decline in sleep quality is a generally accepted modulator of cardiovascular function. During the last decades, there is a growing interest in certain breathing-related sleep disorders, especially obstructive sleep apnea (OSA), due to their established association with major cardiovascular diseases, cardiac arrhythmias, and sudden cardiac death (SCD) [1–4]. In 2005, Gami et al. [5] were the first to emphasize that, in contrast to the general population, the patients with OSA have a peak in sudden cardiac death occurrence at night during sleeping hours, suggesting the involvement of sleep related mechanisms.

Although the exact pathophysiological factors linking OSA and cardiovascular risk are not completely identified so far, several evidences have revealed that chronic sleep fragmentation and intermittent hypoxia may cause a shift in the sympathovagal balance toward a sympathetic predominance and a vagal withdrawal [6], giving rise to increased myocardial electrical instability (MEI).

Myocardial electrical instability, that is, a predisposition to potentially life-threatening ventricular arrhythmias, can be indirectly assessed by numerous noninvasive parameters, including those reflecting ventricular repolarization prolongation and inhomogeneity. Different QT interval dispersion, prolongation, and variability estimation models used in clinical practice have demonstrated their utility for high-risk patient identification over the last two decades [7–9]. Several mathematical formulas have been proposed to describe the physiological pattern of the QT/RR relation and QT interval

heart rate adaptation. Despite the fact that its limitations are often pointed out, Bazett's formula from 1920 is the one used most frequently.

Malik and coauthors [10] have converted several QT/RR regression models (linear, hyperbolic, parabolic, logarithmic, shifted logarithmic, and exponential models) to generic heart rate correction formulas to provide QTc interval values that are independent of the corresponding RR interval values. This approach seems to have created a predisposition for individually optimised heart rate correction.

Beat-to-beat QT interval variability is most often measured using QT variability index (QTVI), proposed by Berger et al. in 1997 [7]. The index quantifies the magnitude of QT interval fluctuations, normalized by both the mean QT duration and the magnitude of heart rate fluctuations. This index has been utilized as a predictor of malignant ventricular arrhythmias in various cardiac and noncardiac conditions, such as congestive heart failure [11], coronary artery disease [12], and panic disorders [13]. Atiga et al. [14] were the first to demonstrate the association between increased level of QT variability and arrhythmic events. In their study, the QTVI was the only clinical variable that identified patients with a previous incidence of SCD in multivariate regression model, outperforming as predictor of several well-known parameters, such as QT interval spatial dispersion, T-wave alternans, ventricular tachycardia inducibility, signal-averaged ECG, heart rate variability, and left ventricular ejection fraction.

Although ventricular repolarization determination methods have been recognized as powerful predictors of SCD in heart disease population, only few studies have examined QT interval properties in OSA patients. In these studies, the results demonstrated QT interval prolongation and increased inhomogeneity [15, 16]. Kilicaslan et al. [17] reported prolongation of a certain QT interval fragment, T-wave peak-to-end, in patients with OSA. Baumert et al. [16] demonstrated that QTVI values, calculated from polysomnographic (PSG) recordings, were associated with sleep apnea severity, but not with sleep stages.

To the best of our knowledge, very limited data [18] is available concerning QT interval duration and variability changes in patients without OSA during various sleep stages. Since rapid eye movement (REM) sleep is characterized by sympathetic surges and elevated sympathetic tone influences both the QT interval duration [19] and QT interval variability [20, 21], the assessment of modulatory effects of various sleep stages on ventricular repolarization parameters per se may add more understanding to arrhythmia genesis in OSA patients.

The novelty of our study lies in applying various QT interval correction formulas and QT variability index while awake and during nonrapid eye movement (NREM) as well as REM sleep stages in nonapneic patients.

The aim of the study was to determine whether different sleep stages, especially REM sleep, affect QT interval duration and variability in male patients without OSA.

2. Methods

2.1. Study Population. The study population included 30 male patients aged between 21 and 60 years who had undergone diagnostic overnight polysomnography for suspected OSA in 2013 and 2014. Patients were selected on the basis of stored PSG recordings and clinical characteristics. The inclusion criteria were as follows: male gender, ECG revealing sinus rhythm, absence of OSA (apnea-hypopnea index < 5), and clinically significant comorbidities, without excessive obesity (defined as BMI $\geq 35\,kg/m^2$). A few patients with treatment-controlled arterial hypertension were included in the study. None of the patients was receiving I and III class antiarrhythmic medications known to affect the QT interval and other drugs that could potentially prolong ventricular repolarization (e.g., antihistaminic, psychotropic, or antibiotic medications). In this study, we did not measure the sleep quality but focused on QT interval within certain sleep stages. To the best of our knowledge, commonly used hypotensive drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta blockers have not demonstrated significant impact on neither QT interval nor sleep stages.

The study was approved by the Tallinn Medical Research Ethics Committee at the National Institute for Health Development.

2.2. Polysomnographic Recordings Analysis and Signal Preprocessing. The PSG data was obtained from routine diagnostic procedures performed at the Mae Pindmaa Sleep Clinic (Tallinn, Estonia). The signals were registered with polysomnography recorder Rembrandt Monet Artist SLP EZ 24 (Medicare Automation B.V., Netherlands). In all patients the following signals were recorded simultaneously: electrooculography (EOG), electrocardiography (ECG), electroencephalography (EEG), submental and anterior tibialis electromyography (EMG), oxygen saturation (SpO_2), oronasal airflow, thoracic and abdominal respiration movements, snoring, and video monitoring. Sampling frequency for physiological signals was 200 Hz. Electrodes and sensors were placed by a professional polysomnography nurse. The duration of the recordings was from 8 to 9 hours. All PSG recordings were analyzed by a well-trained, certified, and experienced sleep technician. Data processing was performed using the Rembrandt Analysis Manager (version 7.5, Medicare Automation B.V., Netherlands). Sleep stages were confirmed manually using standardized procedures in accordance with the technical report of American Academy of Sleep Medicine published in 2007 [22]. Recording segments presenting frequent artefacts were excluded from the analysis. In each recording, two awake, three REM, and three NREM (stage II) sleep episodes (300 seconds each) suitable for processing were selected.

2.3. ECG Recording Analysis. QT interval duration and variability assessment in different sleep stages was performed at polysomnographic ECG lead II. ECG recordings were anonymized and converted to EDF format. Signals were resampled to sampling frequency of 256 Hz due to the EDF format converter provided by producer of PSG recorder. Recorded signals were preprocessed in LabVIEW (National Instruments, USA) environment, applying signal converting

Physionet toolkit [23]. R-peaks were detected and extrasystoles identified using Pan-Tompkins algorithm implemented by P. S. Hamilton (Eplimited Ltd., USA). RR intervals were converted to Normal-to-Normal (NN) intervals. Ectopic beats, as well as pre- and postextrasystolic beats, were excluded from the analysis. T-wave location and type were detected using Ecgpuwave software [24]. As a measure of heart rate variability we computed the standard deviation of normal RR intervals.

We determined mean QT interval duration and T-wave apex to T-wave end interval (Tp-e) duration in all episodes. Only monophasic well-defined T-waves were accepted for measurement. T wave apex and T wave end points' detection were visually verified by an experienced investigator. The end of T wave was determined using the downslope tangent method described previously [25].

QT variability index was evaluated by Berger's formula [7], which is calculated for each subject as the logarithm of the ratio of normalized QT variance to heart rate variance:

$$\mathrm{QTVI} = \log_{10}\left[\frac{\mathrm{QTv}/\mathrm{QTm}^2}{\mathrm{RRv}/\mathrm{RRm}^2}\right]. \quad (1)$$

In this formula, QTv represents the QT interval variance, QTm is the mean QT interval, RRv is the RR interval variance, and RRm is the mean RR interval.

In order to evaluate repolarization duration we calculated average QT interval and corrected QT interval and Tp-e interval—an index considered to reflect transmural dispersion of ventricular repolarization [26]. The average absolute QT interval was normalized for RR interval variations by applying several correction formulas. In addition to Bazett's formula ($\mathrm{QTc} = \mathrm{QT}/\mathrm{RR}^{0.5}$) we used two of six regression formulas proposed by Malik et al. [10]—linear $\mathrm{QTc} = \mathrm{QT} + \alpha \times (1\text{-RR})$ and parabolic $\mathrm{QTc} = \mathrm{QT}/\mathrm{RR}^{\alpha}$. The rationale for choosing specifically these two formulas with two different α values—α minimal and α 0.2—has been presented in our previous publication [27].

2.4. Statistical Analysis. Unless otherwise indicated, the results are presented as means ± standard deviation (SD). Between-group comparisons of variables were carried out using Student's t-test. For the statistical analysis, we used Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA). Two-sided $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Subjects' Characteristics. The investigated population consisted of 30 male (age 40.0 ± 11.5 yr., range 21–60 yr.) subjects. The patients' mean body mass index (BMI) was 26.8 ± 4.8 kg/m^2 and mean apnea-hypopnea index was 1.5 ± 1.4. The mean oxygen saturation values (SpO_2) were during waking 94.8 ± 1.9%, NREM sleep 94.5 ± 1.3%, and REM sleep 94.6 ± 1.6%. Eight patients had treatment-controlled hypertension with an average blood pressure below 140/90 mmHg.

Table 1: Characteristics of heart rate, QT interval duration, and variability in sleep stages.

Variables	Awake	NREM	REM
NN (ms)	962.4 ± 126.3	1032.0 ± 117.5	973.6 ± 109.1
QT mean (ms)	374.6 ± 24.6	389.5 ± 23.1	382.1 ± 23.8
Tp-e (ms)	72.4 ± 7.2	75.9 ± 6.6	74.3 ± 6.4
QTVI	−1.0 ± 0.3	−1.1 ± 0.3	−1.2 ± 0.3

Data are expressed as means ± SD; NREM: nonrapid eye movement sleep stage; REM: rapid eye movement sleep stage; NN: Normal-to-Normal interval; QT: QT interval; Tp-e: T-wave peak to T-wave end interval; QTVI: QT variability index.

Table 2: Characteristics of rate corrected QT intervals in sleep stages.

Variables	Awake	NREM	REM
QTc Bazett mean (ms)	383.7 ± 18.4	384.7 ± 19.9	388.8 ± 19.9
QTc Lin α min mean (ms)	376.2 ± 22.1	389.7 ± 21.7	384.2 ± 21.6
QTc Par α min mean (ms)	376.0 ± 22.3	389.6 ± 21.7	384.1 ± 21.7
QTc Lin α 0.2 mean (ms)	374.5 ± 24.6	389.3 ± 23.0	382.0 ± 23.8
QTc Par α 0.2 mean (ms)	377.9 ± 18.6	387.3 ± 18.9	384.5 ± 19.8

Data are expressed as means ± SD; NREM: nonrapid eye movement sleep stage; REM: rapid eye movement sleep stage; QTc Bazett: rate corrected QT interval based on Bazett's formula; QTc Lin α min: rate corrected QT interval based on linear regression formula α minimum; QTc Par α min: rate corrected QT interval based on parabolic regression formula α minimum; QTc Lin α 0.2: rate corrected QT interval based on linear regression formula α 0.2; QTc Par α 0.2: rate corrected QT interval based on parabolic regression formula α 0.2.

Table 3: The P values of heart rate, QT interval variability, and duration between sleep stages.

Variables	Awake/NREM	Awake/REM	NREM/REM
		P value	
NN	0.03	0.71	0.05
QT mean	0.02	0.23	0.23
Tp-e	0.05	0.28	0.33
QTVI	0.22	0.05	0.45

Significance of differences between sleep stages: $P < 0.05$; REM: nonrapid eye movement sleep stage; REM: rapid eye movement sleep stage; NN: Normal-to-Normal interval; QT: QT interval; Tp-e: T-wave peak to T-wave end interval; QTVI: QT variability index.

3.2. QT Interval Variability and Duration in Different Sleep Stages. The averaged parameters characterizing heart rate and ventricular repolarization in sleep stages are presented in Tables 1 and 2.

The P values of differences in characteristics of heart rate, QT interval variability, and duration are presented in Tables 3 and 4.

3.2.1. NN Interval. A significantly increased mean NN ($P < 0.05$) in NREM sleep in comparison to while awake was present. NN interval means between other sleep stages were not statistically different.

Table 4: The P values of rate corrected QT intervals between sleep stages.

Variables	Awake/NREM	Awake/REM	NREM/REM
		P value	
QTc Bazett mean	0.81	0.30	0.44
QTc Lin α min mean	0.02	0.16	0.34
QTc Par α min mean	0.02	0.16	0.33
QTc Lin α 0.2 mean	0.02	0.23	0.23
QTc Par α 0.2 mean	0.06	0.19	0.58

Significance of differences between sleep stages: $P < 0.05$; REM: nonrapid eye movement sleep stage; REM: rapid eye movement sleep stage; QTc Bazett: rate corrected QT interval based on Bazett's formula; QTc Lin α min: rate corrected QT interval based on linear regression formula α minimum; QTc Par α min: rate corrected QT interval based on parabolic regression formula α minimum; QTc Lin α 0.2: rate corrected QT interval based on linear regression formula α 0.2; QTc Par α 0.2: rate corrected QT interval based on parabolic regression formula α 0.2.

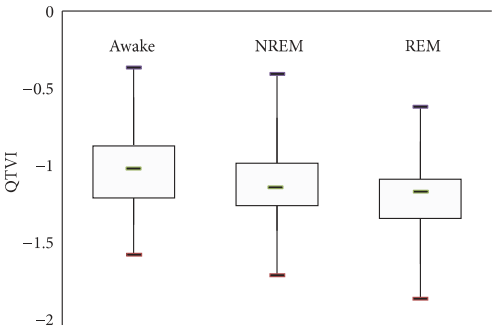

Figure 1: Mean values of QTVI in different sleep stages.

3.2.2. Tp-e Interval. No significant difference between Tp-e interval characteristics was demonstrated.

3.2.3. QT Interval. Mean QT interval duration was significantly shorter ($P < 0.05$) while awake in comparison with NREM sleep (Table 3).

3.2.4. QTVI. Mean values of QTVI while awake, in NREM sleep stage, and in REM sleep stage were -1.0 ± 0.3, -1.1 ± 0.3, and -1.2 ± 0.3, respectively. These values were similar to those of healthy controls reported by Berger et al. (-1.29 ± 0.51) [7] and similar to the weighted mean value (-1.46) for healthy volunteers outlined by Dobson et al. [28]. No statistically significant difference between stages of waking, NREM, and REM was found: P value of waking versus NREM is 0.22; P value of waking versus REM is 0.05; P value of NREM versus REM is 0.45 (Figure 1).

3.2.5. QTc Interval. No difference was detected in mean QT interval duration corrected by Bazett's formula between sleep stages. From the results summarized in Table 4, we can deduce that the corrected QT interval values, corrected by linear (both α minimum and α 0.2) and parabolic (α minimum) regression models, were statistically shorter while awake in comparison with NREM sleep stage ($P < 0.05$).

4. Discussion

In the present study, we investigated the influence of various sleep stages on QT interval variability and duration recorded in nonapneic male subjects. Since the so-called ventricular repolarization reserve is considered to be gender-dependent [18, 29] we included male patients only. Our original approach consisted of simultaneous application of conventional ventricular repolarization duration and variability assessment formulas to polysomnographic ECG recordings at various sleep stages.

The novelty of this study lies in the previously, to the best of our knowledge, unpublished finding that in nonapneic male patients the QT interval variability assessed by QTVI is not affected by REM sleep stage; that is, the repolarization variability is not increased compared to NREM sleep and waking.

4.1. Impact of Various Sleep Stages on the QT Interval Variability Index. Increased temporal ventricular repolarization variability, assessed by QTVI, is convincingly proven to be associated with elevated risk for sudden cardiac death in various cardiac diseases [11, 14, 30–32] and noncardiac conditions [13]. Moreover, it is considered that the augmented QT variance, rather than a drop in heart rate variance, is responsible for increased QTVI in cardiac patients [33]. In recent years, obstructive sleep apnea-related arrhythmogenic risks have increasingly received attention by medical community; at the same time only limited data exist on QTVI as a parameter predicting ventricular arrhythmias in sleep-related breathing disorders [16, 34]. So far, our knowledge concerning the physiological effects of normal sleep on the temporal QT variability is limited. Thus, it is essential to learn more about the fluctuations of this parameter during normal sleep and take such fluctuations into account while interpreting changes in ventricular repolarization in pathological conditions.

It is well known that in alternating sleep stages autonomic cardiac control fluctuates between sympathetic and parasympathetic predominance. The data presented by Somers et al. [35] indicated that in normal subjects sympathetic activity is lower when they are in deep NREM sleep than during waking and REM sleep. Moreover, it is accepted that the sympathetic activity surges during REM sleep can exceed the levels recorded at waking.

QT interval beat-to-beat variability is influenced by multiple factors and, although the mechanisms contributing to variability are not completely understood, elevated sympathetic activity has been considered to be one of the most important among them [20, 36]. Therefore it is tempting to presume that sympathetic bursts in REM sleep have influence on ventricular repolarization temporal lability. However, the results of our study do not prove that sleep stages affect QT variability, at least in subjects without OSA. We suggest that physiological surges (signal inputs) in sympathetic activity characterizing REM sleep do not lead to clinically significant

fluctuations in beat-to-beat dynamicity of ventricular repolarization. Our findings are thus indirectly consistent with the widely accepted opinion that temporal fluctuations in repolarization are aroused by elevated cardiac sympathetic activation in certain pathological conditions only [20, 36]. We conclude that, in the absence of substantial structural and electrical remodeling of myocardium, physiological elevation in sympathetic activity during REM sleep remains subthreshold for clinically significant increase of myocardial electrical instability.

4.2. Impact of Various Sleep Stages on QT and QTc Interval Duration. During continuous ECG recordings, QT interval duration exhibits a well-known circadian pattern reflecting waking- and sleep-induced alterations in ventricular repolarization. Previous studies focusing on the effect of sleep and its stages on the QT interval have established that both QT and QTc intervals are longer at nighttime [16, 18, 37, 38]. In the earlier studies, evaluations were made from 24-hour ECG recordings, where sleep was assumed and changes in sleep stages were not taken into consideration. Gillis et al. [39] studied 8 nonapneic patients with frequent ventricular ectopy at polygraphic monitoring and noted certain prolongation of QT and QTc in NREM as well as REM sleep compared to waking, with no difference between REM and NREM sleep. Unfortunately factors such as small sample size and coexisting cardiac disease limit the interpretation of the data. Lanfranchi et al. [18] investigated healthy individuals free of any sleep disorder using polysomnography and found that the heart rate-corrected QT interval in men remained stable from waking through all sleep stages.

In our study the absolute mean values of QT interval during NREM sleep increased significantly when compared to waking, which can be expected from the relative increase in vagal tone during NREM sleep stage. The differences between waking and REM sleep, as well as between REM and NREM sleep did not reach statistical significance.

Various rate-corrected QT interval formulas grant possibility for obtaining QT values independent of the corresponding RR interval values. The discrepancy among the studies suggests that the formulas have been influenced by the individual differences in the QT/RR relation. In order to determine the dynamics of QT interval, analyzing just RR interval preceding QT interval may be inadequate. The independence of QT interval from previous RR interval can be tested by computing the correlation coefficients. That is why linear and parabolic correction formulas with two different α values were used in our study.

We found that the mean QTc intervals, calculated by different formulas, slightly lengthened in NREM and REM sleep. The difference did not reach statistical significance when Bazett's formula was applied. While using linear and parabolic correction formulas the difference of QTc was significant between waking and NREM sleep in some occasions (Table 4), which according to our opinion is not clinically relevant. On the contrary, the absence of difference of the mean QTc interval values between NREM and REM stages, calculated by all formulas, seems to confirm our conclusion that sympathetic surges during REM stage do not affect repolarization phase.

Finally, some researchers have suggested that prolongation of T-wave apex to T-wave end (Tp-e) interval reflects transmural heterogeneity of ventricular repolarization and can therefore be used as a surrogate marker for risk of elevated reentrant ventricular arrhythmias [26]. Increased Tp-e interval has been reported to be associated with potentially life-threatening ventricular arrhythmias and SCD [40], as well as in patients with moderate-to-severe OSA [17]. That is why we considered it worthwhile to assess the behaviour of this parameter during REM sleep. Similar to the other ventricular repolarization parameters, the mean Tp-e interval was not prolonged at REM sleep as compared to waking or NREM sleep (Table 3).

4.3. Limitations of the Study. We attempted to achieve maximal homogeneity in the physical status of the patients investigated. Nevertheless, a certain number of patients with mild hypertension, although drug-controlled and without clinically detectable left ventricular hypertrophy, were included. Hypertension has been proved to be associated with sympathovagal imbalance [41].

The same applies to obesity. Although we excluded patients with BMI $\geq 35\,kg/m^2$, our patients' mean body mass index $26.8 \pm 4.8\,kg/m^2$ indicates that several patients were clinically overweight. Obesity has been shown to increase QTVI [42]. However, the normal values of QTVI as well as QTc obtained by 5 different regression formulas during REM sleep demonstrate the limited effect of these factors on ventricular repolarization in our study.

It has been reported that REM sleep at the end of the night is characterized by more intensive sympathetic modulation compared to REM sleep that occurs during the first part of the night. From a clinical point of view, this fact can be a potential link between increased sympathetic drive, REM sleep, and the incidence of cardiovascular events in the early morning [43]. We did our best to perform measurements during the REM episodes in the morning hours; however, a few midnight REM episodes were included into data processing. We presume that the limited number of these episodes do not have notable effect on the results.

5. Conclusions

Our results reveal that, in male patients without OSA, different sleep stages do not affect QTVI values. In the absence of notable structural and electrical remodeling of myocardium, physiological elevation in sympathetic activity during REM sleep remains subthreshold concerning clinically significant increase of myocardial electrical instability. Elevated QTVI values found in patients with OSA cannot be interpreted as physiological sympathetic impact during REM sleep and should be considered as a risk factor for potentially life-threatening ventricular arrhythmias. The absence of difference of mean QTc interval values between NREM and REM sleep stages applying all formulas seems to confirm our conclusion that sympathetic surges during REM stage do not induce repolarization variability. Significant difference

in QTc between waking and NREM sleep obtained in our study by certain heart rate correction formulas seems to have no clinical importance as the mean values of the parameter remained in physiological range. The presence and the extent of polysomnographically recorded QTVI and QTc changes in OSA patients require further thorough investigations and require the gender-dependence of these changes.

Conflict of Interests

The authors declare that there is no conflict interests regarding the publication of this paper.

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PUBLICATIONS

Publication II

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Influence of gender on the QT interval variability and duration in different wake–sleep stages in non-sleep apneic individuals: Analysis of polysomnographic recordings

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Abstract

Introduction: The aim of the study was to determine the influence of gender and sleep stages, especially rapid eye movement sleep (REM), on QT interval variability and duration in normal subjects.
Methods: Polysomnographic recordings of 24 male and 24 female patients without obstructive sleep apnea were analyzed. In each patient, the QT interval variability index (QTVI) and the corrected QT interval (QTc) values were calculated as means of 2 awake, 4 non-rapid eye movement sleep (NREM) and 3 REM episodes, 300 s each. For the QTc calculation, five different correction formulas were used.
Results: Gender-related differences in the QT interval variability and duration were detected between all sleep stages ($P < 0.05$). In males, mean values of QTVI while awake, in NREM and REM sleep were -1.1 ± 0.2, -1.1 ± 0.3, -1.3 ± 0.2. In females, mean values of QTVI were -0.9 ± 0.4, -0.9 ± 0.4, and -1.1 ± 0.3, respectively. No difference between sleep stages was detected in the mean values of QTVI and QTc in both groups ($P > 0.05$).
Conclusion: The results of our study demonstrate no significant overall impact of sleep stages on ventricular repolarization variability and duration during physiological sleep in both genders. We found gender differences in the mean values of QTVI and QTc during different sleep stages, which confirm that gender is a modulating factor of ventricular repolarization.

Keywords: QT interval variability index; Rate-corrected QT interval duration; Sleep stages; REM sleep

Introduction

During the last decades, obstructive sleep apnea (OSA) has been associated with the pathogenesis of major cardiovascular diseases, cardiac arrhythmias and sudden cardiac death (SCD) [1–5]. In breathing-related sleep disorders chronic sleep fragmentation and intermittent hypoxia may shift the sympatho-vagal balance toward sympathetic predominance and vagal withdrawal [6] which may predispose to increased myocardial electrical instability. It has been determined that the major subgroups susceptible to adverse influences of surges in sympathetic activity during rapid eye movement (REM) sleep are cardiac [7] and OSA patients [4]. However, the gender dependence of the magnitude and consequences of elevated sympathetic drive during sleep, particularly in REM sleep, are less known. Gender is an important modulating factor of ventricular repolarization, with females having longer action potentials [8], higher susceptibility to several arrhythmias and predisposition to arrhythmogenic effect of certain drugs than the same-aged males [9].

Non-invasive parameters such as elevated ventricular repolarization variability and prolongation have been recognized as powerful predictors of arrhythmic events and SCD in population with heart disease [1,10–13]. OSA-related arrhythmogenic risks have increasingly received attention by medical community, at the same time, only few studies have examined QT interval properties in OSA patients [14,15] and even more limited data [16] concerning the QT interval variability and changes in physiological sleep are available. Since REM sleep is characterized by sympathetic surges and elevated sympathetic tone influences both the QT interval variability and duration, the assessment of modulatory effects of various sleep

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stages on ventricular repolarization parameters in males and females may add more understanding to arrhythmia genesis in OSA patients. To our best knowledge, studies to compare QTVI and various QT interval correction formulas while awake, during non-rapid eye movement (NREM) and REM sleep stages between genders have not been published.

In the present study, we evaluated the gender difference of QT interval variability and duration in different sleep stages by analyzing polysomnographic recordings in normal non-apneic patients.

Methods

Study population

We initially examined the data of 176 (106 men, 73 women) patients from 20 to 80 years referred to the Mae Pindmaa Sleep Clinic (Tallinn, Estonia) between 2013 and 2014 for a polysomnography (PSG) investigation because of clinically suspected breathing-related sleep disorders. The data on the demographics, height, weight, coexisting conditions, and use of medications of each person were collected at the time of PSG. In this study, we first selected 94 (52 man and 42 women) patients without sleep apnea (apnea–hypopnea index <5). We then narrowed the sample by selecting only patients who had body mass index (BMI) ≤ 35 kg/m^2. Of the 88 (52 men and 36 women) remaining patients, 54 (30 men and 24 women) patients who exhibited normal ECG (sinus rhythm, QTc interval duration of <440 ms), had no other clinically significant comorbidities, and were not receiving medications known to affect the QT interval parameters (e.g. I and III class antiarrhythmic, antihistaminic, psychotropic, or antibiotic drugs) were targeted. In this study, male patients were matched by age with an equal number of female patients (24 male and 24 women). The flow diagram of the selection process is shown in Fig. 1.

The study was approved by the Tallinn Medical Research Ethics Committee at the National Institute for Health Development.

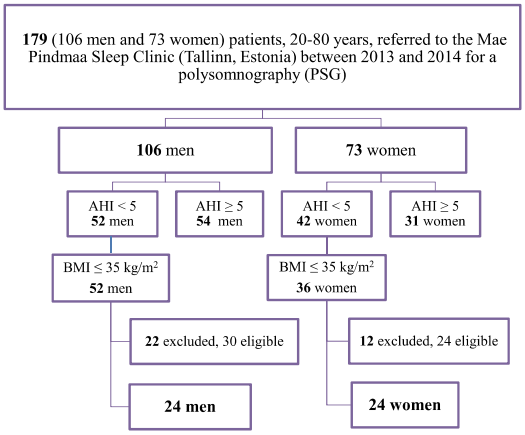

Fig. 1. illustrates the flow diagram of the study population selection process.

Polysomnographic recordings analysis

The PSG recordings were obtained using the polysomnography recorder Rembrandt Monet Artist SLP EZ 24 (Medicare Automation B.V, the Netherlands). In all patients the following signals were simultaneously recorded: electrocardiography, electro-oculography, electroencephalography, submental and anterior tibialis electromyography, arterial oxyhemoglobin saturation (SpO_2), oronasal air flow, thoracic and abdominal respiratory movements, snoring sound, and video monitoring. The duration of the recordings was from 8 to 9 h. The sampling frequency for the physiological signals was 200 Hz. Data processing was performed using the Rembrandt Analysis Manager (version 7.5, Medicare Automation B.V, the Netherlands). Sleep stages were confirmed visually using standardized procedures in accordance with the Technical Report of American Academy of Sleep Medicine published in 2007 [17] by a well-trained, certified, and experienced sleep technician. Recording segments presenting frequent artifacts were excluded from the analysis. In each patient, two awake, four NREM (stage II and III) and three REM sleep episodes (300 s each) suitable for processing were selected.

ECG analysis

The ECG lead II signals from the polysomnograms were anonymized and converted to EDF format. The signals were resampled to sampling frequency of 512 Hz and were pre-processed in LabVIEW (National Instruments, USA) environment, applying the signal converting Physionet toolkit. The R-wave peaks were detected and the extrasystoles identified using Pan-Tompkins algorithm implemented by P. S. Hamilton (Eplimited Ltd., USA). The RR intervals were converted to normal-to-normal intervals. Ectopic beats, as well as pre-and post-extrasystolic beats, were excluded from the analysis. The T-wave location and type were detected using Ecgpuwave software [18]. We measured the mean QT interval duration in all episodes. The T-wave apex and the T-wave end points detection were visually verified by an experienced investigator. Only monophasic well-defined T-waves were accepted. The end of T-wave was determined using the downslope tangent method described previously [19]. The QT variability and QTc analyses were performed for 5-min (300 s) ECG segments. For this analysis we chose two awake episodes (10 min in total), four NREM episodes (15 min stage II and 5 min stage III), and three REM episodes (15 min in total).

The QT variability index was evaluated by the Berger's formula [10], which quantifies the magnitude of the QT interval fluctuations, normalized by both the mean QT duration and the magnitude of heart rate fluctuations. The index is calculated for each subject as the logarithm of the ratio of normalized QT variance to heart rate variance: QTVI = log10 (QTv/QTm^2/RRv/RRm^2). In this formula, QTv represents the QT interval variance, QTm is the mean QT interval, RRv is the RR interval variance, and RRm is the mean RR interval. A single QTVI measurement during 256 s [10] is considered powerful enough to discriminate high-risk patients. To be even more precise, we assessed QTVI in two awake, four NREM and three REM episodes and presented the data as

Table 1
Characteristics of study subjects and quantitative sleep variables.

	Males n = 24		Females n = 24		
	Mean	SD	Mean	SD	*P*-value
Age (yr)	40.0	11.9	43.4	15.2	0.38
BMI (kg/m^2)	26.1	4.2	24.7	4.1	0.26
AHI (n/h)	1.4	1.4	0.9	1.1	0.10
SpO_2 (%)	95.0	1.5	96.0	1.2	0.18
TST (min)	429.8	59.6	391.1	76.9	0.07
NREM (% of TST)	79.1	6.0	78.6	6.4	0.82
REM (% of TST)	18.1	7.2	19.8	6.3	0.40

SD, standard deviation; BMI, body mass index; AHI, apnea–hypopnea index; SpO_2, arterial oxyhemoglobin saturation; TST, total sleep time; NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage.

an average for each stage. Scored events, e.g. arousals, limb movement, were excluded from QTVI assessment.

To evaluate ventricular repolarization duration, the average absolute QT interval was normalized for RR interval variations by applying several correction formulas. Among formulas used to estimate the corrected QT interval (QTc) the Bazett's formula (from 1920) remains, despite its limitations, the one most frequently used: $QTc = QT/RR^{0.5}$. In addition, we used two of six (linear, hyperbolic, parabolic, logarithmic, shifted logarithmic, and exponential models) regression formulas proposed by Malik et al. [20]: linear QTc = QT + α x (1-RR) and parabolic $QTc = QT/RR^{\alpha}$ with two different α- values – α minimal and α 0.2. In order to determine the dynamics of the QT interval, analyzing just RR interval preceding the QT interval may be inadequate. The independence of the QT interval from the previous RR interval can be tested by computing the correlation coefficients. That is why linear and parabolic correction formulas with two different α values were used in our study.

Statistical analysis

Unless otherwise indicated, the results are presented as means ± standard deviation (SD). The normality of study variables was tested with the Kolmogorov–Smirnov test. Mean values of the study population main characteristics and sleep variables were compared between genders using the Student's t-test, except the non-normally distributed apnea–hypopnea index, where the Wilcoxon rank sum test was used. To test the difference between sleep stages within gender we used the Student's t-test. The differences between wake–sleep stages and genders were tested with repeated measures two-way analysis of variance followed by Tukey HSD post-hoc tests for pairwise comparisons of wake–sleep stages. For the statistical analysis, we used the add-in statistics embedded in Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA) and statistical package R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). In all tests two-sided $P \leq 0.05$ was considered statistically significant.

Results

The investigated population consisted of 24 male (age 40.0 ± 11.9 years, range 21–60 years) and 24 female (age 43.4 ± 15.2 years, range 21–72 years) subjects. General characteristics of the study population and quantitative sleep variables are summarized in Table 1.

There were no significant group differences in general characteristics and polysomnographic-measured sleep variables (Table 1). In male subjects, mean values of heart rate while awake, in NREM and REM sleep were 61 ± 7, 58 ± 5, and 62 ± 7. In female subjects, mean values of heart rate while awake, in NREM and REM sleep were 67 ± 6, 65 ± 6, and 65 ± 6, respectively.

The averaged parameters characterizing ventricular repolarization in wake–sleep stages are presented in Table 2.

QT interval variability index

In males, the NN interval was virtually identical in the wake state and in REM sleep but was increased during NREM sleep even though this difference did not meet statistical significance

Table 2
Characteristics of heart rate, QT interval variability and duration in sleep stages.

	Awake					NREM					REM				
	Males		Females			Males		Females			Males		Females		
	Mean	SD	Mean	SD	*P*-value	Mean	SD	Mean	SD	*P*-value	Mean	SD	Mean	SD	*P*-value
MeanNN (ms)	975.5	133.9	895.5	104.9	**0.020**	1031.5	125.0	928.5	89.8	**0.003**	979.0	106.1	922.1	97.6	0.094
SDNN (ms)	55.6	20.7	47.0	21.3	0.219	55.5	19.3	44.2	21.2	0.055	66.8	16.1	61.5	31.9	0.449
MeanQT (ms)	372.2	26.9	382.9	26.1	0.143	385.3	26.3	396.2	25.3	0.136	378.9	23.5	391.5	26.4	0.087
SDQT (ms)	5,7	1.6	6.4	1.6	0.624	5.6	1.9	6.5	1.9	0.154	6.2	0.9	7.1	1.8	0.111
QTVI	−1.1	0.2	−´0.9	0.4	**0.031**	−1.1	0.3	−0.9	0.4	**0.010**	−1.3	0.2	−1.1	0.3	**0.037**
QTc Bazett (ms)	378.9	17.5	406.4	24.8	<**0.001**	380.9	19.7	412.4	21.9	<**0.001**	384.5	18.3	409.4	21.3	<**0.001**
QTc Lin α min (ms)	374.0	23.9	388.5	23.9	**0.036**	385.1	24.8	398.9	23.4	**0.044**	380.7	21.4	395.4	24.6	**0.034**
QTc Par α min (ms)	373.8	24.0	387.9	23.9	**0.040**	385.0	24.8	398.7	23.5	**0.047**	380.7	21.5	395.1	24.7	**0.038**
QTc Lin α 0.2 (ms)	372.3	26.8	383.0	26.0	0.143	372.3	26.8	396.2	25.3	0.135	378.9	23.4	391.5	26.3	0.087
QTc Par α 0.2 (ms)	374.6	19.7	391.9	22.8	**0.006**	383.3	21.0	402.5	22.0	**0.003**	380.9	19.2	398.4	22.0	**0.006**

SD, standard deviation; NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage; meanNN, mean normal-to-normal interval; SDNN, standard deviation of normal-to-normal RR interval; meanQT, mean QT interval; SDQT, standard deviation of meanQT; QTVI, QT variability index; QTc Bazett, rate corrected QT interval based on Bazett's formula; QTc Lin α min, rate corrected QT interval based on linear regression formula α minimum; QTc Par α min, rate corrected QT interval based on parabolic regression formula α minimum; QTc Lin α 0.2, rate corrected QT interval based on linear regression formula α 0.2; QTc Par α 0.2, rate corrected QT interval based on parabolic regression formula α 0.2.
Bold represents the significant p-values.

(P ≥ 0.05). Overall heart rate variability (SDNN) was statistically increased in REM sleep compared to wake and NREM sleep (awake/NREM P = 0.98, awake/REM P = 0.04, NREM/REM P = 0.03).

In females, the NN interval increased during NREM sleep but in REM sleep declined only slightly remaining to the value similar to NREM sleep. NN variability increased significantly in REM sleep when compared to NREM sleep (awake/NREM P = 0.64, awake/REM P = 0.07, NREM/REM P = 0.03).

Females exhibited shorter NN intervals (higher heart rates) than men, this difference reached the statistical significance while awake and during NREM sleep, the gender difference in NN intervals diminished during the REM sleep. Mean NN variability was comparable between males and females (Table 2).

The absolute QT interval increased slightly in NREM and REM sleep compared to wake but did not reach the statistical significance both in males and in females (P ≥ 0.05). QT variability remained unchanged in the wake stage and NREM sleep and mildly (not statistically) increased in REM sleep both in men and women (Fig. 2). The absolute QT interval and QT interval variability did not differ between male and female subjects (Table 2).

A gender dependent difference in the QTVI mean values in different sleep stages was detected (Table 2). Females demonstrated more positive QTVI mean values in all wake–sleep stages, i.e. significantly higher QT interval variability; however, these QTVI values remained in normal range according to the findings of previous studies by Berger (−1.29) [10] and Dobson et al. (−1.46) [21].

No statistically significant difference was found between stages of waking, NREM and REM in both genders: awake vs. NREM P = 0.86 (males); awake vs. REM P = 0.06 (males); NREM vs. REM P = 0.08 (males); awake vs. NREM P = 0.60 (females); awake vs. REM P = 0.20 (females); NREM vs. REM P = 0.06 (females). Thus, the mean values of QTVI did not differ between sleep stages in either of genders.

Rate-corrected QT interval duration

The results show that there are significant differences in the corrected QT interval values between male and female patients in all wake–sleep stages (Table 2), except between values assessed by the linear regression formula with the value of α 0.2.

No difference between sleep stages in the mean QT interval duration corrected by the Bazett's formula, by linear (both α minimum and α 0.2) and parabolic (both α minimum and α 0.2) regression formulas (P > 0.05) was detected in both genders.

Discussion

To elucidate possible sex differences in ventricular repolarization characteristics during sleep, we investigated the influence of sleep stages on the QT interval variability and duration by analyzing ECG from polysomnographic recordings of the normal cohort of non-apneic patients. It is essential to assess the physiological effects of normal sleep on the QT variability and duration in order to take such fluctuations into consideration while interpreting changes in ventricular repolarization in pathological conditions.

Impact of sleep stages on the QT interval variability index

It is generally accepted that certain differences exist in cardiac electrophysiology between women and men. Accumulating evidence suggests that autonomic nervous function differences and hormonal influence on ion-channels' function are among the responsible mechanisms for gender differences in ventricular repolarization and corresponding arrhythmic risk [1,22]. It is considered that female have lower "repolarization reserve" than men and are therefore more susceptible to drug-mediated pro-arrhythmic effects [9]. Nevertheless, there is little evidence addressing the association between the ventricular repolarization parameters and sleep stages.

It is known that the wake stage and REM sleep are the states of sympathetic dominance whereas during NREM sleep with parasympathetic dominance the sympathetic tone is at its lowest [8]. Therefore, it is tempting to presume that fluctuations in autonomic tone, especially sympathetic modulation in REM sleep, have influence on ventricular repolarization lability.

In the present study, we detected a gender dependent difference in the QTVI mean values during all sleep stages but we did not establish differences in QTVI dynamicity between different wake–sleep stages in males and females.

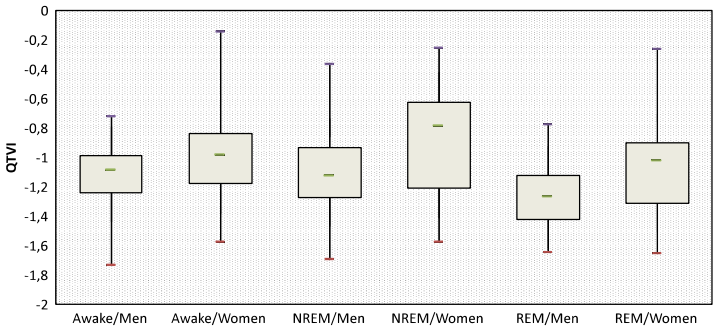

Fig. 2. shows mean QTVI values for both genders. In male subjects, mean values of QTVI while awake, in NREM and REM sleep were −1.1 ± 0.2, −1.1 ± 0.3, −1.3 ± 0.2. In female subjects, the mean values of QTVI while awake, in NREM and REM sleep were −0.9 ± 0.4, −0.9 ± 0.4, and −1.1 ± 0.3, respectively.

Females had more positive QTVI values (higher QTVI interval beat-to-beat variability) in all wake–sleep stages in comparison to men; however, this parameter remained within the normal range in both genders. Our findings demonstrated that heart rate variability was greatest in REM sleep in both genders, likely reflecting the presence of sinus arrhythmia. Also, the QT interval variability slightly mirrored heart rate variability, which is not surprising since in normal subjects mechanisms modulating repolarization should be intact. The higher magnitude of heart rate variability than that of QT variability might suggest that in normal subjects, QT variability do not appear to be influenced by sleep stages and a change in QTVI is rather caused by a change in RR variability.

Thus, our findings are indirectly consistent with a widely accepted opinion that the correlation between sympathetic tone and the increased QT interval variability is strong in the state of high sympathetic activation under certain pathological conditions but might be much weaker under other conditions when autonomic balance is unaffected [7,22,23]. This study permits us to draw inferences that in the absence of substantial structural and electrical remodeling of myocardium, physiological elevation in sympathetic tone during REM sleep remains sub-threshold to affect QTVI. Thus, elevated QTVI values observed in OSA patients cannot be interpreted exclusively as physiological sympathetic impact during REM sleep and should be considered as a risk marker for potentially life-threatening ventricular arrhythmias both in male and female patients.

Impact of wake–sleep stages on the QTc interval duration

The rate-corrected QT interval has been found longer in women compared to men [9,19,24]. Studies investigating the effect of sleep on the QT interval have established that the QT interval duration exhibits circadian pattern; both QT and QTc intervals are longer at night [15,16]. Nevertheless, there is little evidence addressing the association between sleep stages and ventricular repolarization parameters in healthy subjects. Lanfranchi et al. [16] investigated 18 healthy individuals free of any sleep disorders using polysomnography and found that the rate-corrected QT interval in men remained stable through all sleep stages, but in women it significantly increased during REM sleep compared with the waking stage. In our study, the mean values of the QTc interval during NREM and REM sleep were longer than the values observed in the wake stage but the differences of these values calculated by any used formula did not reach statistical significance in either female or male. However, when comparing genders we found significant differences in the corrected QT interval values in every wake–sleep stage.

Limitations

The present study possesses certain limitations that should be taken into account in the interpretation of the results.

An important limitation in this study is that the sample size was relatively small, partly because of the exclusion of patients with poor recording quality aiming to minimize measurement errors. The sample was drawn from individuals referred to the sleep clinic which may limit generalization of our findings. Extrapolation of our findings would require conformation in a broader patient sample. We attempted to achieve maximal homogeneity in the physical status of the patients investigated. Nevertheless, four male and five female patients with mild hypertension, although drug-controlled and without clinically detectable left ventricular hypertrophy, were included. Obesity was over-represented in our study. Even though we excluded patients with BMI $\geq$ 35 kg/m^2, our patients' mean body mass index was 26.8 ± 4.8 kg/m^2 in male and 24.7 ± 4.8 kg/m^2 in female subjects.

Another limitation is related to the technique of the QT interval measurement. Beat-to-beat fluctuations in the QT interval are typically small and measurement technique might have an impact on QT variability measures. We used conventional tangent method for beat-to-beat variability measurement of the QT interval. It has been suggested that conventional methods may provide higher QTVI estimates than template based algorithms, in particular the time shifting algorithm, for beat-to-beat variability measurement of QT [1]. We have to mention a limitation, which is relevant for not measuring in this study the influence of T wave amplitude on QT variability metrics. Since the inverse relationship between QT interval variability and T wave amplitude potentially confounds QT variability assessment, reporting QT variability in relation to the T wave amplitude is recommended [1].

Conclusion

The results of our study demonstrate no significant overall impact of sleep stages on the ventricular repolarization variability and duration. The absence of difference in the mean QT variability index and QTc interval values between sleep stages in male and female subjects indicates that physiological sympathetic surges during the REM stage do not have significant adverse effect on the ventricular repolarization. After all, we found gender differences in the absolute mean values of QTVI and QTc during wake–sleep stages, which confirm that gender is a modulating factor of ventricular repolarization. However, these effects appear to have little clinical importance as these parameters remained within physiological range.

We conclude that in the absence of notable structural and electrical remodeling of myocardium, physiological elevation in sympathetic activity during REM sleep remains sub-threshold concerning clinically significant increase of myocardial electrical instability. Elevated QTVI and/or QTc values in patients with OSA should not be attributed to the impact of sympathetic surge during REM sleep and may be risk markers for potentially life-threatening ventricular arrhythmias.

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Original Article

QT interval variability index and QT interval duration during different sleep stages in patients with obstructive sleep apnea

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ABSTRACT

Objectives: The aim of the study was to investigate the impact of obstructive sleep apnea (OSA) on the QT interval variability and duration in patients during different sleep stages.
Methods: Polysomnographic recordings of 28 (13 male, 15 female) patients with OSA and 30 (15 male, 15 female) patients without OSA were analyzed. The QT interval variability index (QTVI) and the corrected QT interval (QTc) analyses were performed using two awake, 3–4 non-rapid eye movement (NREM) and three rapid eye movement (REM) sleep episodes (each 300 s). The Bazett formula, linear, and parabolic heart rate correction formulas with two separate α values were used.
Results: QTVI was statistically higher in OSA than in non-OSA patients for males while awake (awake -0.7 ± 0.3 vs -1.2 ± 0.2, $p = 0.001$; NREM -0.9 ± 0.4 vs -1.1 ± 0.3, $p = 0.110$; REM -1.1 ± 0.3 vs -1.3 ± 0.2, $p = 0.667$) and for females in all wake–sleep stages (awake -0.3 ± 0.7 vs -0.9 ± 0.5, $p = 0.001$; NREM -0.3 ± 0.5 vs -0.8 ± 0.4, $p = 0.002$; REM -0.3 ± 0.5 vs -1.0 ± 0.4, $p < 0.001$). QTVI was significantly higher during awake compared to sleep stages in OSA males ($p < 0.05$); no difference between wake–sleep stages was found in females ($p > 0.05$). Significant gender differences in QTVI existed in OSA patients during sleep ($p < 0.05$) but not while awake. No significant differences in QTc between patients groups were observed.
Conclusions: OSA is associated with increased QT variability. REM sleep per se does not increase QTVI. In OSA patients, QTVI might be a more useful measure to detect ventricular repolarization abnormality than measures of QTc.

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder that plays an important role in the occurrence of cardiovascular diseases and sudden cardiac death (SCD) [1–3]. The apnea–hypopnea index (AHI) and nocturnal hypoxemia strongly predict SCD independent of other well-established risk factors [4]. In contrast to the general population, incidences of SCD in individuals with OSA typically peak during the night [5].

The association between the presence of OSA and abnormalities in cardiac electrophysiological parameters has been investigated, including increased QT interval variability [6] and prolonged QT [7,8]. Although the exact pathophysiological factors linking OSA and ventricular arrhythmias are not conclusively identified, previous studies have demonstrated an important role for sympathetic activation in the development of lethal ventricular arrhythmias. Chronic sleep fragmentation and intermittent hypoxia may shift the sympatho-vagal balance toward sympathetic predominance and a vagal withdrawal [9], which may predispose to increased myocardial electrical instability.

Although the number of studies on applying noninvasive electrocardiographic markers for arrhythmogenic risk stratification continues to grow, it is still unknown whether different QT interval variability and prolongation estimation formulas can provide valuable prognostic information in the OSA population and whether sleep stages and gender differences can have an impact on their clinical utility.

The novelty of our study lies in applying the QT variability index and various QT interval correction formulas on polysomnographic recordings during sleep stages in sleep apneic patients.

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The aim of this study was to explore whether male and female patients with OSA are more likely to have increased QT interval variability and duration during different sleep stages.

2. Methods

2.1. Study population

The initial study population included 106 male and 73 female patients referred to the Mae Pindmaa Sleep Clinic (Tallinn, Estonia) between 2013 and 2014 for polysomnography (PSG) because of clinically suspected breathing-related sleep disorders. The data on the demographics, height, weight, coexisting conditions, and use of medications of each person were collected at the time of PSG. In the initial study population, OSA was diagnosed in 85 patients (54 men and 31 women) based on apnea–hypopnea index (AHI) $\geq$5 [10]. A total of 94 patients (52 men and 42 women) with AHI <5 were considered as the non-OSA group. The following exclusion criteria within the OSA and non-OSA groups were applied: evidence of cardiac, pulmonary or central nervous system disease; poor ECG signal quality; use of medications known to affect the QT interval parameters (eg, I and III class antiarrhythmic, antihistaminic, psychotropic, or antibiotic drugs); insufficient length of analyzable sleep stage; abnormal electrocardiography (ECG) findings (eg, nonsinus rhythm, intraventricular conduction delay, QTc interval duration of >440 milliseconds). Well-controlled arterial hypertension without clinically detectable left ventricular hypertrophy was not considered an exclusion criterion.

The study was approved by the Tallinn Medical Research Ethics Committee at the National Institute for Health Development.

2.2. Polysomnographic recording analysis

Overnight polysomnography was performed using standard methods and the PSG recorder Rembrandt Monet Artist SLP EZ 24 (Medicare Automation B.V, the Netherlands). Recordings for each person included electroencephalography, electro-oculography, submental and anterior tibialis electromyography, electrocardiography, pulse oximetry, oronasal air flow, thoracic and abdominal respiratory movements, snoring sound, and video monitoring. The polysomnographic recordings were scored by a certified sleep technologist and verified by sleep physicians according to the American Academy of Sleep Medicine criteria [11]. An apnea was defined as the absence of nasal air flow for $\geq$10 s in the presence of respiratory efforts. Hypopnea was defined as a $\geq$50% reduction in respiratory airflow lasting for more than 10 s, accompanied by a $\geq$4% decrease in oxygen saturation. The apnea–hypopnea index was calculated as the number of episodes of apnea and hypopnea per hour of sleep. The following data for each patient were collected: age, gender, body mass index (BMI), total sleep time, NREM and REM sleep as percentages of the total sleep time, the mean oxygen desaturation time.

The sampling frequency for the physiological signals was 200 Hz. Data processing was performed using the Rembrandt Analysis Manager (version 7.5, Medicare Automation B.V, the Netherlands). The original purpose was to select randomly at least two awake, four non-rapid eye movement (NREM) and three rapid eye movement (REM) sleep episodes (300 consecutive seconds) for further processing in each patient.

2.3. ECG analysis

Electrocardiographic signals (lead II) from the selected episodes of polysomnograms were anonymized, converted to EDF format, and resampled to sampling frequency of 512 Hz. The recorded signals were pre-processed in LabVIEW (National Instruments, USA) environment, applying the signal converting Physionet toolkit. The R-wave peaks were detected and the extrasystoles identified using Pan-Tompkins algorithm implemented by P. S. Hamilton [12]. Ectopic beats, as well as pre- and post-extrasystolic beats, were excluded from the analysis. The T-wave location and type were detected using Ecgpuwave software [13]. The T-wave apex and the T-wave end point detection were visually verified by a single experienced observer. The end of the T-wave was determined by the tangent method [14] as the intersection of the tangent of the downslope of the T-wave with the isoelectric baseline. Only monophasic well-defined T-waves were accepted.

The algorithm proposed by Berger et al. [15] was used to measure the QT variability index:

$$QTVI = \log_{10}\left(\frac{\frac{QTv}{QTm^2}}{\frac{RRv}{RRm^2}}\right), \quad (1)$$

where *QTv* represents the QT interval variance, *QTm* is the mean QT interval, *RRv* is the R–R interval variance, and *RRm* is the mean R–R interval. The QTVI index quantifies the magnitude of the QT interval fluctuations, normalized by both the mean QT duration and the magnitude of heart rate fluctuations. A single QTVI measurement during 256 s [15] is considered powerful enough to discriminate high-risk patients.

The average absolute QT was normalized for variations of RR by applying correction models as follows: nonlinear, with the Bazett formula

$$QTc = \frac{QT}{RR^{0.5}}; \quad (2)$$

two regression formulas proposed by Malik et al. [16], namely, linear

$$QTc = QT + \alpha\cdot(1 - RR) \quad (3)$$

and parabolic

$$QTc = \frac{QT}{RR^{\alpha}}. \quad (4)$$

In order to determine the dynamics of the QT interval, analyzing only the RR interval preceding the QT interval may be inadequate, which is why linear and parabolic correction formulas with two different α values were used in our study.

2.4. Statistical analysis

Unless otherwise indicated, the results are presented as mean ± standard deviation (SD). The normality of study variables was checked visually and tested with the Kolmogorov–Smirnov test. Mean values of the study population main characteristics were compared between OSA and non-OSA groups using the Student *t*-test, except non-normally distributed apnea–hypopnea index, for which the Wilcoxon rank sum test was used. Heart rate variability, QT interval variability and duration differences between OSA and non-OSA groups, wake–sleep stages, and genders were tested with repeated-measures full factorial three-way analysis of variance followed by Tukey HSD post hoc tests for pairwise comparisons. All study variables except normal-to-normal interval were right skewed and were logarithm transformed to achieve normality before applying analysis of variance. Statistical analysis was performed using Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA) and statistical package R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). In all tests, two-sided p values $\leq$ 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population

In this study, 58 subjects aged 21–73 years were enrolled: 28 patients (13 men, 15 women) with OSA and 30 subjects (15 men, 15 women) without OSA. Baseline characteristics and sleep measurements of patients with and without OSA are presented in Table 1.

There were no significant differences between OSA and non-OSA males in terms of the mean age but females with OSA were older than females without OSA ($p = 0.026$). As expected, patients with OSA had a higher BMI and AHI and lower SpO_2 when compared with patients without OSA. Sleep structure was similar in all groups, including total sleep time and percentage of NREM and REM sleep (Table 1).

There were no significant differences between female and male patients with OSA, except with regard to age ($p = 0.002$).

A total of 25 patients (17 in the OSA and eight in the non-OSA group) had well-controlled hypertension in their anamnesis.

3.2. QT interval variability index between OSA and non-OSA patients

The averaged parameters characterizing heart rate variability and QT variability in the wake stage and sleep stages are presented in Table 2.

The median and interquartile range of SDNN (reflecting the overall heart rate variability) and SDQT (reflecting QT variability without normalization to heart rate) are demonstrated for study groups in Fig. 1.

QTVI values in OSA patients were more positive than those in non-OSA subjects in wake–sleep stages. Between-group analysis of variance revealed that the mean QTVI was statistically greater (ie, more positive) in OSA patients than in non-OSA patients for females in all sleep stages but for males only while awake (Fig. 2).

3.3. QT interval variability index between females and males with OSA

When comparing females and males with OSA, females exhibited lower NN variability (SDNN) than males; this difference reached statistical significance during NREM and REM sleep (awake vs NREM, $p = 0.852$l; awake vs REM, $p = 0.008$; NREM vs REM, $p = 0.010$). Females exhibited statistically higher QT variability (SDQT) than males in all sleep stages (awake vs NREM, $p = 0.002$; awake vs REM, $p = 0.003$; NREM vs REM, $p = 0.001$).

Females demonstrated more positive QTVI mean values in all wake–sleep stages, this was true also for subjects without OSA (Table 1). A gender difference in the QTVI mean values in OSA patients reached statistical significance in NREM sleep ($P < 0.001$) and REM sleep ($P < 0.001$), but not while awake ($P = 0.085$) (Fig. 3).

3.4. QT interval variability index between sleep stages in patients with OSA

Between sleep stages analysis of variance revealed that in male patients with OSA, the QTVI mean values were significantly higher during awake periods compared to sleep stages (awake vs NREM, $p = 0.013$; awake vs REM, $p < 0.001$; and NREM vs REM, $p = 0.174$). No statistical difference was found when assessing the QTVI mean values in females with OSA (awake vs NREM, $p = 0.919$; awake vs REM, $p = 0.843$; and NREM vs REM, $p = 0.985$).

3.5. Rate-corrected QT interval duration

The averaged parameters characterizing ventricular repolarization duration in wake–sleep stages are presented in Table 3. A comparison of OSA and non-OSA patients revealed no significant differences in the QT interval mean values corrected by any formulas (Table 3).

4. Discussion

The main findings from the study are as follows:

- Beat-to-beat repolarization variability was increased in patients with OSA compared to patients without OSA.
- Female patients with OSA appear to have more positive values of the QT interval variability index (QTVI) than do males.
- In OSA patients, REM sleep per se does not increase QT variability.
- In sleep apnea patients, QTVI might be a more useful measurement to detect ventricular repolarization abnormality than measures of QTc.

Noninvasive evaluation of myocardial vulnerability may help detect patients who are at high risk for malignant cardiac arrhythmias. In the present study, we investigated the influence of obstructive sleep apnea on QT interval variability and duration in male and female patients. Our particular approach consisted of simultaneous application of conventional ventricular repolarization variability and duration assessment formulas to polysomnographic ECG recordings at various sleep stages.

Table 1
Characteristics of the study subjects.

Characteristic	Males, $n = 28$					Females, $n = 30$				
	OSA $n = 13$		Non-OSA $n = 15$		p	OSA $n = 15$		Non-OSA $n = 15$		p
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (y)	47.5	11.7	39.2	12.1	0.078	60.9	9.4	51.5	12.4	**0.026**
BMI (kg/m^2)	32.5	2.7	26.0	4.1	**<0.001**	33.2	6.1	25.5	2.9	**<0.001**
AHI (n/h)	31.2	18.1	1.2	1.0	**<0.001**	19.7	19.8	1.0	1.2	**<0.001**
SpO_2 (%)	90.9	7.8	95.4	0.9	**0.034**	92.4	1.4	95.3	1.4	**<0.001**
HR (beats/min)	65.2	8.0	60.3	3.7	0.072	67.9	6.9	64.1	5.9	0.094
TST (min)	433.7	32.0	413.4	54.7	0.251	400.0	40.8	382.3	90.6	0.498
NREM (% of TST)	81.0	5.0	79.0	5.2	0.322	83.1	4.8	80.1	6.3	0.158
REM (% of TST)	18.7	5.8	18,0	6.2	0.744	15.9	4.4	18.7	6.2	0.181

Bold represents significant p values. AHI, apnea–hypopnea index; BMI, body mass index; HR, heart rate; NREM, non-rapid eye movement sleep stage; REM, rapid eye movement sleep stage; SpO_2, arterial oxyhemoglobin saturation; TST, total sleep time.

Table 2
Characteristics of heart rate variability and QT interval variability in wake–sleep stages.

	Sleep stage	Males, $n = 28$					Females, $n = 30$				
		OSA $n = 13$		Non-OSA $n = 15$		p	OSA $n = 15$		Non-OSA $n = 15$		p
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
MeanNN (ms)	Awake	869.0	119.7	949.0	128.8	0.054	861.3	96.9	916.8	100.1	0.163
	NREM	909.5	126.0	1005.8	127.0	0.022	884.5	88.1	943.8	88.1	0.136
	REM	942.5	124.2	946.2	106.7	0.596	922.9	77.6	935.8	95.6	0.743
SDNN (ms)	Awake	33.2	17.4	56.5	18.0	**<0.001**	30.9	11.4	45.9	24.5	**0.042**
	NREM	52.0	27.0	56.1	13.5	0.315	32.5	12.5	46.3	22.1	**0.044**
	REM	66.5	27.1	68.0	15.8	0.667	42.7	12.3	56.9	25.4	0.146
MeanQT (ms)	Awake	365.3	23.8	373.0	23.0	0.465	384.8	19.4	387.4	29.1	0.848
	NREM	377.9	22.5	386.4	21.8	0.437	401.9	51.0	396.6	29.4	0.737
	REM	379.9	24.7	380.5	19.4	0.943	409.1	55.7	391.4	29.5	0.161
SDQT (ms)	Awake	6.0	1.4	5.8	1.9	0.723	13.5	19.4	6.4	1.7	**0.004**
	NREM	6.8	2.8	5.9	2.3	0.373	11.4	6.3	6.4	2.3	**<0.001**
	REM	7.2	2.4	6.2	1.4	0.397	12.5	7.1	6.8	2.2	**<0.001**
QTVI	Awake	−0.7	0.4	−1.2	0.2	**0.001**	−0.3	0.7	−0.9	0.5	**0,001**
	NREM	−0.9	0.4	−1.1	0.3	0.11	−0.3	0.5	−0.8	0.4	**0,002**
	REM	−1.1	0.3	−1.3	0.2	0.667	−0.3	0.5	−1.0	0.4	**<0.001**

Bold represents significant p values. MeanNN, mean normal-to-normal interval; MeanQT, mean QT interval; NREM, non-rapid eye movement; QTVI, QT variability index; REM, rapid eye movement; SDNN, standard deviation of normal-to-normal RR interval; SDQT, standard deviation of MeanQT.

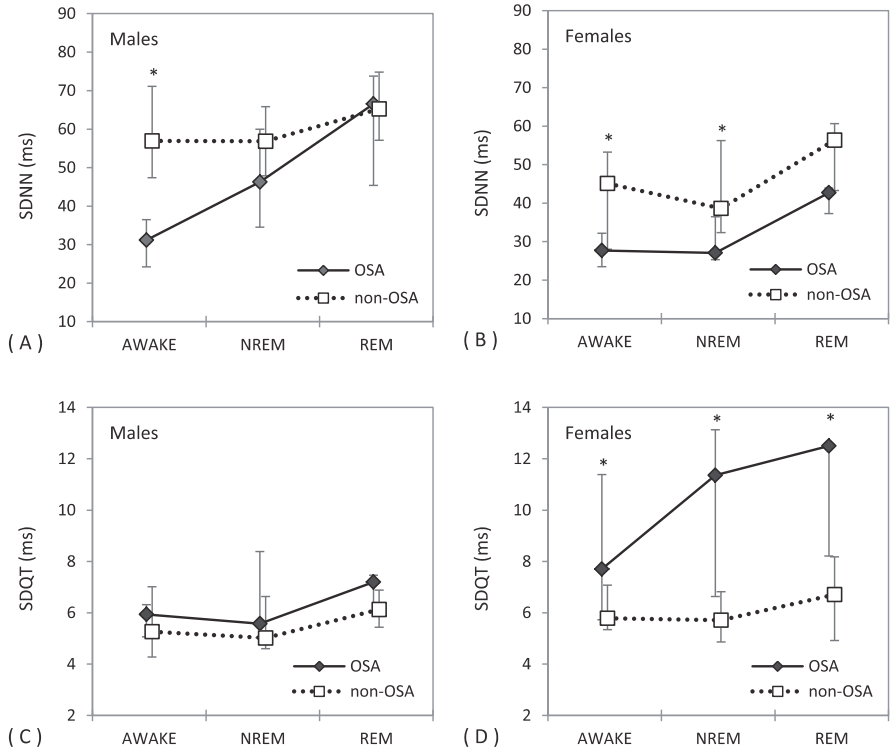

Fig. 1. Median and interquartile range of NN interval (SDNN) and QT interval (SDQT) in male and female patients with and without obstructive sleep apnea (OSA) in the wake stage, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Asterisks denote statistically significant ($p < 0.05$) differences between OSA and non-OSA patients (based on logarithm-transformed data using analysis of variance followed by Tukey test for pairwise comparisons).

4.1. QT interval variability index

Increased beat-to-beat ventricular repolarization variability, assessed by QTVI, has been associated with malignant ventricular arrhythmias and sudden cardiac death in various cardiac diseases [15,17–23]. There is growing evidence of OSA-related arrhythmogenic risks and SCD [24]; simultaneously, only limited published data exist on QTVI as a parameter predicting ventricular

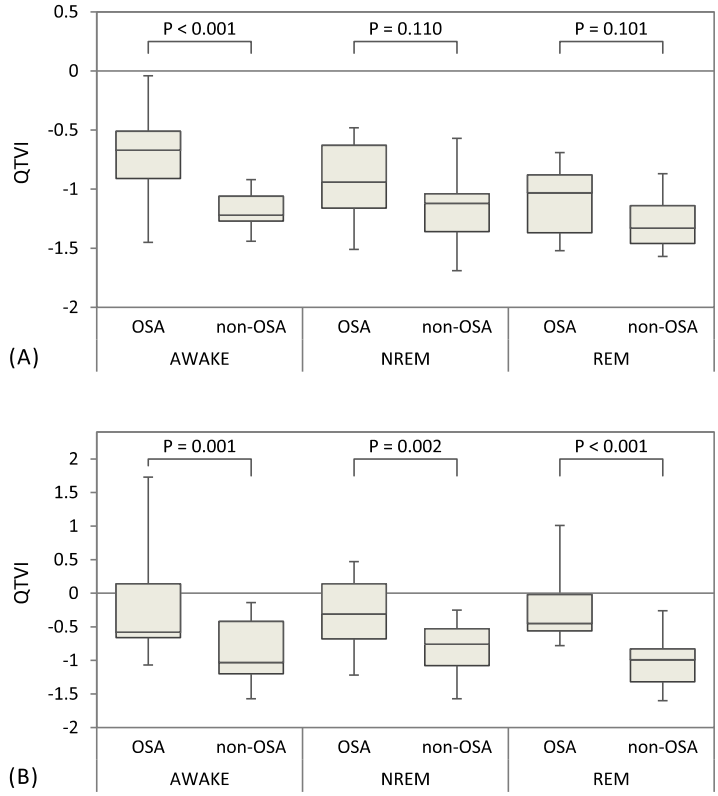

Fig. 2. QT variability index (QTVI) distributions for (A) male and (B) female patients with obstructive sleep apnea (OSA) and without OSA. *p* Values are calculated based on logarithm-transformed data using analysis of variance followed by Tukey test for pairwise comparisons.

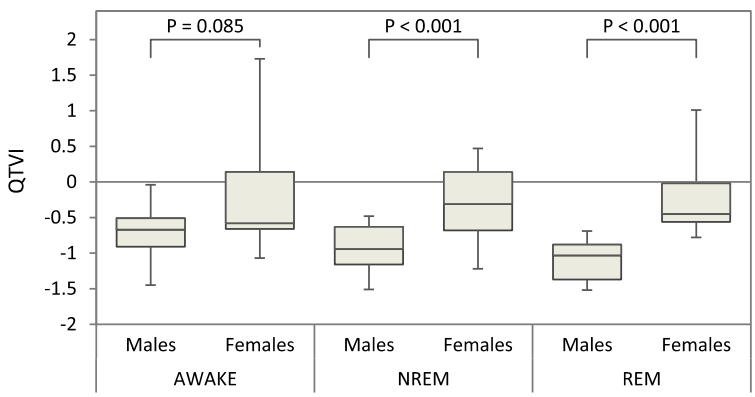

Fig. 3. QT variability index (QTVI) distributions in obstructive sleep apnea (OSA) patients for male and female patients. *p* Values are calculated based on logarithm-transformed data using analysis of variance followed by Tukey test for pairwise comparisons.

arrhythmias in sleep-related breathing disorders [6]. Therefore, it is essential to learn more about the fluctuations of this parameter during sleep stages in patients with obstructive sleep apnea and to evaluate it separately in men and women.

The results of our study are generally in line with previous data by Baumert et al. [6] demonstrating that OSA is associated with changes in QT interval variability during sleep, and that the variance of beat-to-beat QT intervals correlates more strongly with the

Table 3
Characteristics of the QT interval duration in wake–sleep stages.

	Sleep stage	Males, $n = 28$					Females, $n = 30$				
		OSA $n = 13$		Non-OSA $n = 15$		p	OSA $n = 15$		Non-OSA $n = 15$		p
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
QTc Bazett (ms)	Awake	393.4	10.3	385.0	15.2	0.385	416.3	23.8	405.8	22.6	0.284
	NREM	398.4	19.0	387.0	12.6	0.248	429.8	64.3	409.0	18.6	0.079
	REM	393.3	15.4	389.1	12.7	0.667	428.3	58.1	405.7	17.5	0.046
QTc Lin α min (ms)	Awake	372.7	18.7	375.7	20.2	0.769	392.2	19.5	390.7	25.9	0.858
	NREM	382.6	20.4	386.5	19.6	0.698	408.6	50.8	398.7	26.9	0.424
	REM	383.2	21.7	382.7	16.6	0.975	412.1	49.9	393.9	26.9	0.104
QTc Par α min (ms)	Awake	371.9	19.1	375.3	20.5	0.731	391.6	19.3	390.4	26.2	0.882
	NREM	382.1	20.5	386.4	19.6	0.669	408.6	50.7	398.5	27.1	0.447
	REM	383.0	21.9	382.6	16.7	0.979	411.8	50.1	393.7	27.1	0.108
QTc Lin α 0.2 (ms)	Awake	365.3	23.7	373.0	22.9	0.461	384.8	19.4	387.4	29.1	0.847
	NREM	377.9	22.5	386.4	21.8	0.432	401.9	51.0	396.6	29.4	0.733
	REM	380.0	24.7	380.5	19.3	0.943	409.9	52.1	391.5	29.5	0.129
QTc Par α 0.2 (ms)	Awake	376.0	16.9	377.5	15.5	0.871	396.9	17.8	394.5	24.7	0.767
	NREM	385.7	17.0	386.4	14.3	0.932	412.7	55.1	401.4	24.1	0.347
	REM	385.0	18.0	383.7	13.7	0.905	417.0	53.7	396.9	23.6	0.066

NREM, non-rapid eye movement; QTc Bazett, rate corrected QT interval based on Bazett's formula; QTc Lin α min, rate corrected QT interval based on linear regression formula α minimum; QTc Par α min, rate corrected QT interval based on parabolic regression formula α minimum; QTc Lin α 0.2, rate corrected QT interval based on linear regression formula α 0.2; QTc Par α 0.2, rate corrected QT interval based on parabolic regression formula α 0.2; REM, rapid eye movement.

severity of OSA than standard measures of heart rate variability and is correlated with blood oxygenation but not sleep stage. In the present study, we found increases in QTVI (more positive QTVI values) in patients with OSA compared to non-OSA patients for both genders. In males, this difference reached statistical significance only while awake, but in females in all wake–sleep stages. Heart rate variability was significantly reduced while awake in patients with OSA compared to non-OSA patients. At the same time, increased QT variability was observed only in female patients with OSA.

QT interval temporal beat-to-beat variability is influenced by multiple factors, although the mechanisms contributing to this pathological phenomenon are not completely determined, and conclusive evidence demonstrating a primary etiological role for OSA in ventricular arrhythmias is not yet available. Elevated sympathetic activity has been considered to be one of the most important reasons for temporal fluctuations in repolarization, but in certain pathological conditions only [25,26]. Data presented by Somers et al. [27] indicated that, in normal subjects, sympathetic activity is lower when they are in deep NREM sleep than during awake periods and REM sleep. It is tempting to presume that bursts of sympathetic nerve activity in REM sleep may have an additional adverse influence on ventricular repolarization temporal lability in patients with OSA. This hypothesis did not receive support from our observations; the results of our study do not demonstrate a significant additional increase in QT interval variability in REM sleep compared to the awake stage and NREM sleep.

It is considered that autonomic nervous function differences and hormonal influence on ion-channel function are among the responsible mechanisms for gender differences in ventricular repolarization and corresponding arrhythmic risk [17]. To determine the gender difference in QTVI among OSA patients, we compared the mean values of QT interval variability between each wake–sleep stage. Females demonstrated more positive QTVI mean values in all wake–sleep stages, although the statistically significant difference was reached only for NREM and REM sleep. The interpretation of this result was quite difficult, as the female patients were older than the male patients. The higher age at the time of diagnosis of OSA in females could be associated with the greater prevalence of this disorder after menopause or failing to seek help earlier for symptoms suggestive of OSA. Age-related reduction in RR variance could increase QTVI values [28], but it is not considered to be a significant factor contributing to increased QTVI [29]. Furthermore, 12 female and five male patients with OSA had well-controlled hypertension and no signs of detectable left ventricular hypertrophy. Hypertension has been proved to be associated with increased QTVI [30].

4.2. Rate-corrected QT interval duration

The QT interval prolongation corrected for heart rate (QTc) is considered to be a marker of risk for arrhythmias and death. Several studies have associated the QTc interval with the risk of both arrhythmias and SCD in the general population [31,32] and in patients with cardiovascular disease [33]. The data on increased QTc in OSA are rather inconclusive. Prolonged QT intervals in OSA patients have been reported [34]. Rossi et al. [7] found, in a randomized trial, that in patients with moderate to severe symptomatic OSA, 2 weeks of continuous positive airway pressure (CPAP) withdrawal led to significant prolonging of QTc. Shamsuzzman et al. [35] showed that OSA in either men or women was associated with a significant increase in resting daytime QTc. Also, Barta et al. [36], studying the effect of sleep apnea, demonstrated that nocturnal QTc interval did not show any significant change compared to 24-hour periods, and they did not find an increased risk of ventricular arrhythmias.

In our study, we compared the changes in the QTc interval during awake and sleep periods between OSA and non-OSA patients. The results of our study showed that both males and females with OSA did not have significantly increased QTc compared to the respective non-OSA groups.

The results of this study are based on simultaneous application of generally approved ventricular repolarization variability and duration assessment formulas to polysomnographic ECG recordings at various wake–sleep stages. To gain more insight into their role in identifying myocardial electrical instability in sleep apnea patients, sleep stages and male and female gender were assessed separately. Our results showed that OSA affected mainly QT variability but that there was no significant impact on QT duration. QTVI was elevated in OSA patients compared with normal subjects, especially while awake.

4.3. Clinical implications

Our study results have brought us a step closer to understanding beat-to-beat fluctuations in ventricular repolarization in OSA and

non-OSA patients. We found that QTVI was elevated in OSA patients compared with normal subjects. Elevated QTVI has been reported as a marker of cardiac arrhythmias. Our results suggest that special attention should be paid to detect cardiac arrhythmias in patients with sleep apnea, especially in obese women at older ages. The absence of difference of the mean QTc interval values between OSA and non-OSA males and females, calculated by all formulas, seems to confirm our conclusion that QTVI is more valuable prognostic measurement than QTc for risk stratification in OSA patients.

The insights gained from this work should stimulate the development of further studies to asses the clinical utility of QT interval variability measurement for risk stratification. Large-sample prospective studies are needed to confirm the relationship between QTVI and cardiac arrhythmias in OSA patients, as well as the impact of OSA treatment with CPAP.

4.4. Limitations of the study

Certain limitations should be taken into account when interpreting the results of the present study. First, the number of patients is relatively small and is drawn from individuals referred to a sleep clinic, which may limit the generalization of our findings. We cannot exclude the possibility of gender difference in QTVI due to the limited statistical power of the sample. Second, we used a conventional tangent method for beat-to-beat variability measurement of the QT interval, which may provide higher QTVI estimates than template-based algorithms [17]. Also, we did not measure the influence of T-wave amplitude on QT variability metrics. Finally, we included patients with a wide spectrum of AHI values.

5. Conclusion

Obstructive sleep apnea is associated with increased QT interval variability. REM sleep per se does not increase QT variability. In sleep apnea patients, QTVI might be more useful measure to detect ventricular repolarization abnormality than measures of QTc. The issue of whether the observed alteration in QTVI is associated with a higher incidence of cardiac arrhythmia and sudden cardiac death in OSA patients should be addressed in a prospective study.

Acknowledgements

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Conflict of interest

The authors declare that there are no conflicts of interests regarding the publication of this paper.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2017.06.026.

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APPENDIX 2

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Education

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George Washington University	2004	Clinical exercise physiology, master degree
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Language competence

Language	Level
Estonian	Mother tongue, fluent
English	Fluent
Russian	Average

Professional employment

Period	Organization	Position
2017…	East Tallinn Central Hospital (University of Tartu)	Resident physician
2014-2017	Institute of Cardiology Polyclinic, LTD	Consulting physician
2009-2017	Tallinn Health Care College	Head of the Health Promotion Department
2006-2008	Ministry of Social Affairs, Department of Public Health	Chief specialist
2006-2007	Audentes Sports School	Lecturer
2004-2006	Estonian Antidoping Center	Director
2002	George Washington University, Women Exercise Research Centre	Intern
2001	Centre of Elite Sports Research	Physician
1994-1997	Estonian Institute of Cardiology	Physician
1992-1994	Emergency Hospital of Tallinn	Intern

Research activity

Analysis of ventricular repolarization electrical signals in patients with and without obstructive sleep apnea by polysomnographic recordings.

Supervised thesis

Hele-Tea Riik, MSc. Pulse arrival time measurement in polysomnographic recordings. TUT, 2017.

APPENDIX 3

ELULOOKIRJELDUS

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Keel	Tase
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2017…	Ida-Tallinna Keskhaigla (Tartu Ülikool)	Arst-resident
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2009-2017	Tallinna Tervishoiu Kõrgkool	Tervisedenduse õppetooli juhataja
2006-2008	EV Sotsiaalministeerium, rahvatervise osakond	Peaspetsialist
2006-2007	Audentese Spordikool	Lektor
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Teadustegevus

Ventrikulaarse repolarisatsiooni elektriliste signaalide analüüsimine obstruktiivse uneapnoega ja apnoeta patsientidel polüsomnograafiliste salvestuste põhjal.

Juhendatud lõputöö

Hele-Tea Riik, MSc. Pulssilaine saabumisaja mõõtmine polüsomnograafiliste signaalide põhjal. TUT, 2017.